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(GB). **SCOCCHETTI, Tiziana** [IT/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).

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(74) Agent: **RUTTER, Keith**; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BIT, Rino, Antonio** [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). **GIBLIN, Gerard, Martin, Paul** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **HALL, Adrian** [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). **HURST, David, Nigel** [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). **KILFORD, Ian, Reginald** [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). **MILLER, Neil, Derek** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW

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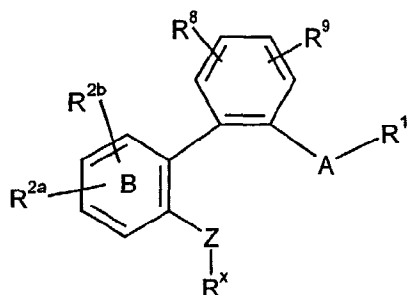
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(54) Title: PHENYL COMPOUNDS



(I)

(57) Abstract: Compounds of formula (I) or derivatives thereof: wherein A, B, Z, R<sup>1</sup>, R<sup>2a</sup>, R<sup>2b</sup>, R<sup>x</sup>, R<sup>8</sup>, and R<sup>9</sup> are as defined in the specification, a process for the preparation of such compounds, pharmaceutical compositions comprising such compounds and the use of such compounds in medicine.

## PHENYL COMPOUNDS

This invention relates to phenyl derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, in particular  
5 their use in the treatment of conditions mediated by the action of PGE<sub>2</sub> at the EP<sub>1</sub> receptor.

The EP<sub>1</sub> receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE<sub>2</sub>. PGE<sub>2</sub> also has affinity for the other EP receptors (types EP<sub>2</sub>, EP<sub>3</sub> and EP<sub>4</sub>). The EP<sub>1</sub> receptor is associated with smooth muscle contraction, pain (in particular  
10 inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion. We have now found a novel group of compounds which bind with high affinity to the EP<sub>1</sub> receptor.

A number of review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists:  
15 *Eicosanoids; From Biotechnology to Therapeutic Applications*, Folco, Samuelsson, Macclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and *Journal of Lipid Mediators and Cell Signalling*, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function*, S Narumiya et al, *Physiological Reviews* 1999, 79(4), 1193-126.  
20 An article from *The British Journal of Pharmacology* (1994, 112, 735-740) suggests that Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) exerts allodynia through the EP<sub>1</sub> receptor subtype and hyperalgesia through EP<sub>2</sub> and EP<sub>3</sub> receptors in the mouse spinal cord. Furthermore an article from *The Journal of Clinical Investigation* (2001, 107 (3), 325) shows that in the EP<sub>1</sub> knock-out mouse pain-sensitivity responses are reduced by approximately 50%. Two papers from *Anesthesia and Analgesia* have shown that (2001, 93, 1012-7) an EP<sub>1</sub> receptor antagonist (ONO-8711)  
25 reduces hyperalgesia and allodynia in a rat model of chronic constriction injury, and that (2001, 92, 233-238) the same antagonist inhibits mechanical hyperalgesia in a rodent model of post-operative pain. S. Sarkar et al in *Gastroenterology*, 2003, 124(1), 18-25 demonstrate the efficacy of EP<sub>1</sub> receptor antagonists in the treatment of visceral pain in a human model of hypersensitivity. Thus, selective prostaglandin ligands, agonists or antagonists, depending  
30 on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based  
35 side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects. Moreover, by sparing potentially beneficial prostaglandin pathways, these agents may have enhanced efficacy over NSAIDs and/or  
40 COX-2 inhibitors.

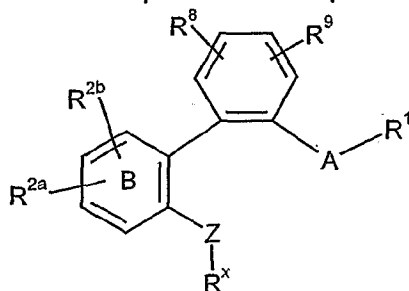
In *The American Physiological Society* (1994, 267, R289-R-294), studies suggest that PGE<sub>2</sub>-induced hyperthermia in the rat is mediated predominantly through the EP<sub>1</sub> receptor.

WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996), EP 752421-A1 (January 08, 1997) and WO 01/19814 (22 March 2001) disclose compounds as being useful in the treatment of prostaglandin mediated diseases.

- 5 P. Lacombe *et al* (220th National Meeting of The American Chemical Society, Washington D.C., USA, 20-24 August, 2000) disclosed 2,3-diarylthiophenes as potent ligands for the human EP<sub>1</sub> prostanoid receptor. By way of comparison the terphenyl compound 2-benzyloxy[1,1';2',1'']terphenyl-4''-carboxylic acid was also disclosed, but the presented data suggested that this terphenyl compound was less potent and less selective than the  
10 comparable 2,3-diarylthiophene compound.

It is now suggested that a novel group of phenyl derivatives surprisingly are selective for the EP<sub>1</sub> receptor over the EP<sub>3</sub> receptor, and are therefore indicated to be useful in treating conditions mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors. Such conditions include pain,  
15 or inflammatory, immunological, bone, neurodegenerative or renal disorders.

Accordingly the present invention provides a compound of formula (I):



(I)

wherein:

- 20 A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;  
B represents a phenyl or pyridyl ring;  
Z represents O, S, SO, or SO<sub>2</sub>;  
R<sup>1</sup> represents CO<sub>2</sub>R<sup>4</sup>, CN, CONR<sup>5</sup>R<sup>6</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>4</sup>, optionally substituted alkyl, optionally  
25 substituted alkenyl, optionally substituted SO<sub>2</sub>alkyl, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>CONR<sup>5</sup>R<sup>6</sup>, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;  
R<sup>2a</sup> and R<sup>2b</sup> independently represents hydrogen, halogen, optionally substituted alkyl, optionally substituted alkoxy, CN, SO<sub>2</sub>alkyl, SR<sup>5</sup>, NO<sub>2</sub>, optionally substituted aryl, CONR<sup>5</sup>R<sup>6</sup>  
30 or optionally substituted heteroaryl;  
R<sup>x</sup> represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR<sup>4</sup>, O and SO<sub>n</sub>, wherein n is 0, 1 or 2: or R<sup>x</sup> represents optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocyclyl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-bicyclic heterocyclyl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-aryl;  
35 R<sup>4</sup> represents hydrogen or an optionally substituted alkyl;

- R<sup>5</sup> represents hydrogen or an optionally substituted alkyl;  
 R<sup>6</sup> represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO<sub>2</sub>aryl, optionally substituted SO<sub>2</sub>alkyl, optionally substituted SO<sub>2</sub>heteroaryl, CN, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>aryl, optionally substituted  
 5 CQ<sup>a</sup>Q<sup>b</sup>heteroaryl or COR<sup>7</sup>;  
 R<sup>7</sup> represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;  
 R<sup>8</sup> and R<sup>9</sup> independently represent hydrogen, chloro, fluoro, CF<sub>3</sub>, C<sub>1-3</sub>alkoxy or C<sub>1-3</sub>alkyl;  
 Q<sup>a</sup> and Q<sup>b</sup> are independently selected from hydrogen and CH<sub>3</sub>;  
 10 wherein when A is a 6-membered ring the R<sup>1</sup> substituent and phenyl ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R<sup>1</sup> substituent and phenyl ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;  
 and derivatives thereof;  
 15 provided that the compound is not 2-benzyloxy[1,1';2',1'']terphenyl-4"-carboxylic acid.

Preferably when A is a 6-membered ring, the R<sup>1</sup> substituent and phenyl ring are attached to carbon atoms 1,2-, or 1,3- relative to each other.

- 20 Suitably A includes phenyl, naphthyl, pyridyl, pyridazinyl, pyrazinyl or pyrimidinyl, all of which may be optionally substituted. Preferably A is phenyl, pyridyl or pyrazinyl, all of which may be optionally substituted. More preferably A is optionally substituted pyridyl or optionally substituted pyrazinyl.
- 25 Optional substituents for A include up to four substituents, preferably 0 or 1 substituent, independently selected from halogen, CN, optionally substituted CO<sub>2</sub>C<sub>1-6</sub>alkyl, CONR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>R<sup>6</sup>, optionally substituted NR<sup>5</sup>COC<sub>1-6</sub>alkyl, optionally substituted NR<sup>5</sup>COPhenyl, optionally substituted NR<sup>5</sup>COPiperidinyl, optionally substituted NR<sup>5</sup>COheterocyclyl, optionally substituted NR<sup>5</sup>SO<sub>2</sub>C<sub>1-6</sub>alkyl, OH, optionally substituted OC<sub>1-6</sub>alkyl, optionally substituted C<sub>1-6</sub>alkyl and NR<sup>10</sup>R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> together with the nitrogen atom to which they are  
 30 attached form a morpholine ring, a 5- or 6-membered lactam ring or a 5- or 6-membered cyclic sulphonamide, wherein R<sup>5</sup> and R<sup>6</sup> are as defined above for compounds of formula (I).

- Suitably optional substituents for A include halogen, CN, CO<sub>2</sub>C<sub>1-4</sub>alkyl, CONR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>R<sup>6</sup>,  
 35 NR<sup>5</sup>COC<sub>1-4</sub>alkyl optionally substituted by NH<sub>2</sub>, phenyl, thienyl, OC<sub>1-4</sub>alkyl or OCH<sub>2</sub>phenyl, NR<sup>5</sup>COPhenyl, optionally substituted NR<sup>5</sup>COPiperidinyl, e.g. NHCO-1-acetylpiperidinyl, NHCO-dimethylisoxazolyl, NR<sup>5</sup>SO<sub>2</sub>C<sub>1-4</sub>alkyl, OC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl and 2-oxopyrrolidinyl, wherein R<sup>5</sup> and R<sup>6</sup> are as defined above for compounds of formula (I).

- 40 Preferred optional substituents for A include F, Cl, CN, CO<sub>2</sub>C<sub>1-4</sub>alkyl, CONH<sub>2</sub>, CONHC<sub>1-4</sub>alkyl, CONHCH<sub>2</sub>CH<sub>2</sub>OH, CONHCH<sub>2</sub>pyridyl, NH<sub>2</sub>, NHCOC<sub>1-4</sub>alkyl, NHCOCH<sub>2</sub>NH<sub>2</sub>, NHCOPhenyl, NHCO-dimethylisoxazolyl, NHCO-1-acetylpiperidinyl,

NHCOCH<sub>2</sub>OCH<sub>2</sub>phenyl, NHCOCH<sub>2</sub>phenyl, NHCOCH<sub>2</sub>OC<sub>1-4</sub>alkyl, NHCOCH<sub>2</sub>thienyl, NHSO<sub>2</sub>C<sub>1-4</sub>alkyl, OC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl, and 2-oxopyrrolidinyl.

5 In an alternative aspect optional substituents for A when a phenyl group include up to four substituents, preferably 0 or 1 substituent, independently selected from halogen, NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>COC<sub>1-6</sub>alkyl, NR<sup>5</sup>SO<sub>2</sub>C<sub>1-6</sub>alkyl, OR<sup>5</sup>, C<sub>1-6</sub>alkyl and NR<sup>10</sup>R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> together with the nitrogen atom to which they are attached form a morpholine ring, a 5- or 6-membered lactam ring or a 5- or 6-membered cyclic sulphonamide, wherein R<sup>5</sup> and R<sup>6</sup> are as defined above for compounds of formula (I). Alternative optional substituents for A are selected from  
10 halogen, NR<sup>5</sup>R<sup>6</sup>, NHCOC<sub>1-6</sub>alkyl, NHSO<sub>2</sub>C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl and NR<sup>10</sup>R<sup>11</sup>.

Optional substituents for A when a 5- or 6-membered heterocyclyl group include NH<sub>2</sub>. When A is pyridyl it may be substituted on the ring nitrogen by an oxygen to give a pyridine N-oxide.

15 When B is pyridyl, preferably the pyridine N atom is positioned 1,2- relative to the ring carbon carrying either the phenyl or Z substituent.

In a preferred aspect at least one of the A and B rings contain a nitrogen atom.

20 Suitably Z is O.

Suitably R<sup>1</sup> includes CO<sub>2</sub>H, optionally substituted CONHSO<sub>2</sub>aryl, CH<sub>2</sub>CO<sub>2</sub>H, SO<sub>2</sub>NHCOR<sup>7</sup>, SO<sub>2</sub>NHCOC<sub>1-6</sub>alkyl or tetrazolyl. Preferably R<sup>1</sup> includes CO<sub>2</sub>H, CONHSO<sub>2</sub>phenyl,  
25 CONHSO<sub>2</sub>(4-nitrophenyl), CH<sub>2</sub>CO<sub>2</sub>H, SO<sub>2</sub>NHCOphenyl, SO<sub>2</sub>NHCOC<sub>1-4</sub>alkyl or tetrazolyl.

Alternatively R<sup>1</sup> includes CO<sub>2</sub>R<sup>4</sup>, CONHSO<sub>2</sub>aryl, CH<sub>2</sub>CO<sub>2</sub>R<sup>4</sup>, SO<sub>2</sub>NHCOR<sup>7</sup>, SO<sub>2</sub>NHCOC<sub>1-6</sub>alkyl or tetrazolyl.

30 Preferably R<sup>1</sup> represents CO<sub>2</sub>H.

Preferably R<sup>2a</sup> is hydrogen.

Preferably R<sup>2b</sup> represents hydrogen, halogen, CF<sub>3</sub>, optionally substituted C<sub>1-6</sub>alkyl, CN or  
35 SO<sub>2</sub>C<sub>1-6</sub>alkyl, more preferably R<sup>2b</sup> represents hydrogen, halogen, or CF<sub>3</sub>.

Preferably R<sup>2b</sup> is positioned 1,4- relative to the Z substituent and 1,3- relative to the phenyl ring.

40 Suitably R<sup>x</sup> includes optionally substituted C<sub>1-8</sub>alkyl, optionally substituted CH<sub>2</sub>phenyl, CH<sub>2</sub>pyridyl, or CH<sub>2</sub>thienyl. Preferably R<sup>x</sup> represents C<sub>1-8</sub>alkyl, optionally substituted CH<sub>2</sub>phenyl or CH<sub>2</sub>thienyl, most preferably R<sup>x</sup> represents C<sub>1-8</sub>alkyl or optionally substituted CH<sub>2</sub>phenyl.

Suitably optional substituents for  $R^x$  when  $\text{CH}_2\text{phenyl}$  include one to three substituents selected from Cl, F, Br, and  $\text{CF}_3$ . Particular examples include Cl and F.

- 5 When  $R^x$  is  $\text{C}_{1-8}\text{alkyl}$  examples include propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, 3-methylbutyl, cyclopentylmethyl and cyclohexylmethyl.

Suitably  $R^4$  includes hydrogen and  $\text{C}_{1-6}\text{alkyl}$ . Preferably  $R^4$  is hydrogen.

- 10 Suitably  $R^5$  includes hydrogen and  $\text{C}_{1-6}\text{alkyl}$ . Preferably  $R^5$  is selected from hydrogen and  $\text{C}_{1-3}\text{alkyl}$ .

Suitably  $R^6$  includes hydrogen,  $\text{C}_{1-6}\text{alkyl}$  optionally substituted by phenyl, thienyl, pyridyl, or OH,  $\text{SO}_2\text{phenyl}$  and  $\text{COR}^7$ .

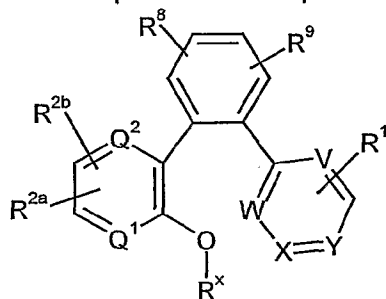
- 15 Suitably  $R^7$  includes hydrogen, phenyl and  $\text{C}_{1-6}\text{alkyl}$ .

Suitably  $R^8$  and  $R^9$  include hydrogen, chloro, fluoro,  $\text{CF}_3$ ,  $\text{OCH}_3$  and  $\text{CH}_3$ . In one alternative  $R^8$  and  $R^9$  are each hydrogen.

- 20 An example of  $Q^a$  is hydrogen.

An example of  $Q^b$  is hydrogen.

- 25 In one aspect the present invention provides a compound of formula (Ia):



(Ia)

wherein:

W, X, and Y each represents  $\text{CR}^{12}$  or N;

V represents  $\text{CR}^1$ ,  $\text{CR}^{12}$  or N;

- 30 wherein at least two of W, X, Y or V is  $\text{CR}^{12}$ ; and  $R^{12}$  is independently selected from hydrogen, halogen, CN, optionally substituted  $\text{CO}_2\text{C}_{1-6}\text{alkyl}$ ,  $\text{CONR}^5\text{R}^6$ ,  $\text{NR}^5\text{R}^6$ , optionally substituted  $\text{NR}^5\text{COC}_{1-6}\text{alkyl}$ , optionally substituted  $\text{NR}^5\text{COphenyl}$ , optionally substituted  $\text{NR}^5\text{COpiperidiny}$ , optionally substituted  $\text{NR}^5\text{COheterocycl}$ , optionally substituted  $\text{NR}^5\text{SO}_2\text{C}_{1-6}\text{alkyl}$ , OH, optionally substituted  $\text{OC}_{1-6}\text{alkyl}$ , optionally substituted  $\text{C}_{1-6}\text{alkyl}$  and  $\text{NR}^{10}\text{R}^{11}$ ;
- 35  $Q^1$  and  $Q^2$  each represents CH, or one of  $Q^1$  and  $Q^2$  is N and the other is CH;

- R<sup>1</sup> is CO<sub>2</sub>H, optionally substituted CONHSO<sub>2</sub>aryl, CH<sub>2</sub>CO<sub>2</sub>H, SO<sub>2</sub>NHCOR<sup>7</sup>, SO<sub>2</sub>NHCOC<sub>1-6</sub>alkyl or tetrazolyl and is positioned 1,2-, or 1,3- relative to the phenyl ring;  
 R<sup>2a</sup> and R<sup>2b</sup> are independently selected from hydrogen, halo, or CF<sub>3</sub>;  
 R<sup>x</sup> represents optionally substituted C<sub>1-6</sub>alkyl, or R<sup>x</sup> represents optionally substituted  
 5 CQ<sup>a</sup>Q<sup>b</sup>-heterocyclyl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-phenyl wherein Q<sup>a</sup> and Q<sup>b</sup> are independently selected from hydrogen and CH<sub>3</sub>;  
 R<sup>4</sup> represents hydrogen or an optionally substituted C<sub>1-6</sub>alkyl;  
 R<sup>5</sup> represents hydrogen or an optionally substituted C<sub>1-6</sub>alkyl;  
 R<sup>6</sup> represents hydrogen or an optionally substituted C<sub>1-6</sub>alkyl, optionally substituted  
 10 SO<sub>2</sub>phenyl, optionally substituted SO<sub>2</sub>heterocyclyl group, CN, optionally substituted CH<sub>2</sub>phenyl or COR<sup>7</sup>;  
 R<sup>7</sup> represents hydrogen, optionally substituted heteroaryl or optionally substituted phenyl;  
 R<sup>8</sup> and R<sup>9</sup> independently represent hydrogen, chloro, fluoro, CF<sub>3</sub>, C<sub>1-3</sub>alkoxy or C<sub>1-3</sub>alkyl;  
 and  
 15 R<sup>10</sup> and R<sup>11</sup> together with the nitrogen atom to which they are attached form a morpholine ring, a 5- or 6-membered lactam ring or a 5- or 6-membered cyclic sulphonamide, and derivatives thereof.

- Suitably R<sup>x</sup> includes C<sub>1-6</sub>alkyl, CH<sub>2</sub>thienyl or CH<sub>2</sub>phenyl optionally substituted by one, two or  
 20 three substituents selected from CF<sub>3</sub> and halogen, e.g. Br, Cl and F.

In one aspect R<sup>1</sup> is positioned 1,3- relative to the phenyl ring.

- In another aspect at least one of W, X, Y and V is N.  
 25

In yet another aspect one of Q<sup>1</sup> and Q<sup>2</sup> is N.

- A particular set of compounds are those wherein one or two of W, X, Y and V is N and Q<sup>1</sup>  
 and Q<sup>2</sup> are both CH; or one of Q<sup>1</sup> and Q<sup>2</sup> is N and W, X, Y, and V are each CR<sup>12</sup>.  
 30

Preferably Q<sup>1</sup> is N or CH and Q<sup>2</sup> is CH.

- Suitably R<sup>12</sup> includes hydrogen, halogen, CN, CO<sub>2</sub>C<sub>1-4</sub>alkyl, CONR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>COC<sub>1-4</sub>alkyl  
 optionally substituted by NH<sub>2</sub>, phenyl, thienyl, OC<sub>1-4</sub>alkyl or OCH<sub>2</sub>phenyl, NR<sup>5</sup>Cophenyl,  
 35 optionally substituted NR<sup>5</sup>COpiperidinyl, e.g. NHCO-1-acetylpiperidinyl, NHCO-  
 dimethylisoxazolyl, NR<sup>5</sup>SO<sub>2</sub>C<sub>1-4</sub>alkyl, OC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl and 2-oxopyrrolidinyl, wherein R<sup>5</sup> and  
 R<sup>6</sup> are as defined above for compounds of formula (I).

- Particular examples of R<sup>12</sup> include hydrogen F, Cl, CN, CO<sub>2</sub>C<sub>1-4</sub>alkyl, CONH<sub>2</sub>, CONHC<sub>1-4</sub>  
 40 alkyl, CONHCH<sub>2</sub>CH<sub>2</sub>OH, CONHCH<sub>2</sub>pyridyl, NH<sub>2</sub>, NHCOC<sub>1-4</sub>alkyl, NHCOCH<sub>2</sub>NH<sub>2</sub>,  
 NHCophenyl, NHCO-dimethylisoxazolyl, NHCO-1-acetylpiperidinyl,  
 NHCOCH<sub>2</sub>OCH<sub>2</sub>phenyl, NHCOCH<sub>2</sub>phenyl, NHCOCH<sub>2</sub>OC<sub>1-4</sub>alkyl, NHCOCH<sub>2</sub>thienyl,  
 NHSO<sub>2</sub>C<sub>1-4</sub>alkyl, OC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl, and 2-oxopyrrolidinyl.

When one or two of W, X, Y and V is N, examples of  $R^{12}$  include hydrogen and  $NH_2$ .

Preferably  $R^{2a}$  is hydrogen.

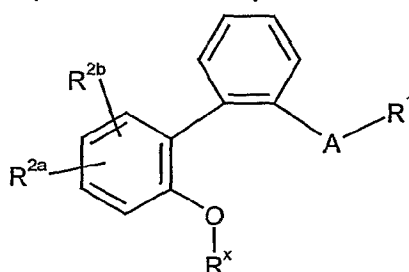
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Preferably  $R^{2b}$  is positioned 1,4- relative to  $OR^x$  and 1,3- relative to the phenyl ring.

Preferably  $R^{2b}$  is selected from F, Cl, Br and  $CF_3$ .

10 In one aspect  $R^8$  and  $R^9$  are both hydrogen.

In an alternative aspect the present invention provides compounds of formula (Ib):



(Ib)

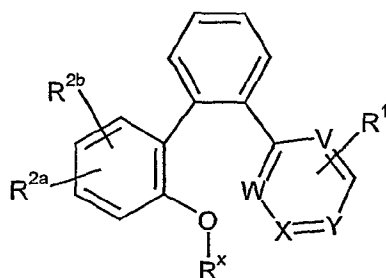
wherein:

- 15 A represents optionally substituted phenyl, an optionally substituted 5- or 6- membered heterocyclyl ring or an optionally substituted bicyclic heterocyclyl group;  
 $R^1$  represents hydrogen,  $CO_2R^4$ ,  $CONR^5R^6$ ,  $CH_2CO_2R^4$ , optionally substituted  $C_{1-6}$ alkyl, optionally substituted  $C_{1-6}$ alkenyl, optionally substituted  $SO_2C_{1-6}$ alkyl,  $SO_2NR^5R^6$ ,  $NR^5CONR^5R^6$ ,  $CONR^5R^6$ , 2H-tetrazol-5-yl-methyl or optionally substituted heterocyclyl;  
 20 wherein when A is a 6-membered ring the  $R^1$  and phenyl group are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the  $R^1$  and phenyl group are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;  
 $R^{2a}$  and  $R^{2b}$  independently represent hydrogen, halo,  $CF_3$ , optionally substituted  $C_{1-6}$ alkyl, CN,  $SO_2R^5$ ,  $NO_2$ , optionally substituted aryl,  $CONR^5R^6$  or optionally substituted heteroaryl;  
 25  $R^x$  represents optionally substituted  $C_{1-8}$ alkyl wherein 1 or 2 of the non-terminal carbon atoms may optionally be replaced by a group independently selected from  $NR^4$ , O or  $SO_n$ , wherein n is 0, 1 or 2; or  $R^x$  may be optionally substituted  $CQ_2$ -heterocyclyl or optionally substituted  $CQ_2Ph$  wherein each Q is independently selected from H and  $CH_3$ ;  
 30  $R^4$  represents hydrogen or an optionally substituted  $C_{1-6}$ alkyl;  
 $R^5$  represents hydrogen or an optionally substituted  $C_{1-6}$ alkyl;  
 $R^6$  represents hydrogen, optionally substituted  $C_{1-6}$ alkyl, optionally substituted  $SO_2$ aryl, optionally substituted  $SO_2$ heterocyclyl group, CN or  $COR^7$ ;  
 $R^7$  represents optionally substituted aryl or heteroaryl;  
 35 and derivatives thereof.



In one aspect the derivatives are pharmaceutically acceptable derivatives.

Examples of compounds of formula (Ib) are compounds of formula (Ic):



(Ic)

wherein:

$R^1$  is  $\text{CO}_2R^4$ ,  $\text{CONHSO}_2\text{Ph}$ ,  $\text{CH}_2\text{CO}_2R^4$ ,  $\text{SO}_2\text{NHCOPh}$ ,

$\text{SO}_2\text{NHCOC}_{1-6}\text{alkyl}$  or tetrazolyl;

$R^{2a}$  and  $R^{2b}$  are independently selected from hydrogen, halo, or  $\text{CF}_3$ ;

$R^x$  represents optionally substituted  $\text{C}_{1-8}\text{alkyl}$ , or  $R^x$  may be optionally substituted  $\text{CQ}_2$ -heterocycl or optionally substituted  $\text{CQ}_2$ -phenyl wherein Q is independently selected from hydrogen and  $\text{CH}_3$ ;

$R^4$  is hydrogen or an optionally substituted  $\text{C}_{1-6}\text{alkyl}$ ;

W, X, Y and V represents CH or N wherein at least one of W, X, Y or V is CH;

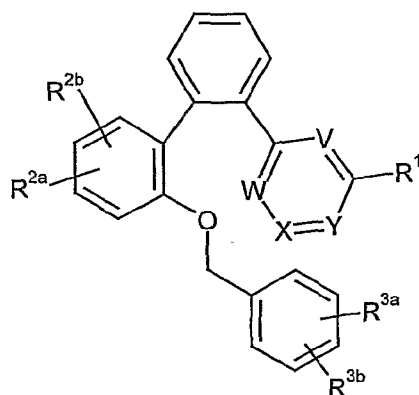
or derivatives thereof.

In one aspect the derivatives are pharmaceutically acceptable derivatives.

Examples of  $R^x$  include  $\text{C}_{1-8}\text{alkyl}$  or optionally substituted  $\text{CH}_2\text{phenyl}$ .

Preferably  $R^4$  is hydrogen.

In another aspect the compounds of formula (I) include compounds of formula (Id):



(Id)

$R^1$  is  $\text{CO}_2R^4$ ;

$R^{2a}$  and  $R^{2b}$  are independently selected from hydrogen, halo, optionally substituted  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{CF}_3$ , CN or  $\text{SO}_2\text{C}_{1-6}\text{alkyl}$ ;

R<sup>3a</sup> and R<sup>3b</sup> are independently selected from hydrogen, halo or optionally substituted OC<sub>1-6</sub>alkyl;

R<sup>4</sup> is hydrogen or an optionally substituted C<sub>1-6</sub>alkyl, preferably hydrogen;

W, X, Y and V represents CH or N wherein at least one of W, X, Y or V is CH;

5 and derivatives thereof.

In one aspect the derivatives are pharmaceutically acceptable derivatives.

In another aspect W, X, Y and V each represents CH.

10

Preferably R<sup>3a</sup> and R<sup>3b</sup> independently represent hydrogen, halo or optionally substituted O(C<sub>1-6</sub>)alkyl, more preferably hydrogen or halo.

15

Examples of the compounds of formula (I) include the compounds of Examples 1 to 90 and derivatives thereof.

In one aspect examples of compounds of formula (I) include:

2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3"-carboxylic acid;

(2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3"-yl)-acetic acid;

20 (2-benzyloxy-5-chloro[1,1';2',1'']terphenyl-2"-yl)acetic acid;

(2-benzyloxy-5-chloro[1,1';2',1'']terphenyl-4"-yl)acetic acid;

5"-acetylamino-2-benzyloxy-5-chloro[1,1';2',1'']terphenyl-3"-carboxylic acid;

2-benzyloxy-5-chloro-5"-propionylamino[1,1';2',1'']terphenyl-3"-carboxylic acid;

25 2-benzyloxy-5-chloro-5"-(2-methylpropanoylamino)-[1,1';2',1'']terphenyl-3"-carboxylic acid;

2-benzyloxy-5"-butyrylamino-5-chloro[1,1';2',1'']terphenyl-3"-carboxylic acid;

2-benzyloxy-5-chloro-5"-[(1-phenyl-methanoyl)amino]-[1,1';2',1'']terphenyl-3"-carboxylic acid;

2-benzyloxy-5-chloro-5"-methanesulfonylamino-[1,1';2',1'']terphenyl-3"-carboxylic acid

5"-amino-2-benzyloxy-5-chloro[1,1';2',2'']-3"-carboxylic acid;

30 2-benzyloxy-5"-butyrylamino-5-trifluoromethyl[1,1';2',1'']terphenyl-3"-carboxylic acid-3-carboxylic acid;

2-benzyloxy-4"-chloro[1,1';2',1'']terphenyl 2"-carboxylic acid;

2-benzyloxy-5"-fluoro-[1,1';2',1'']terphenyl-2"-carboxylic acid;

2-benzyloxy-4"-fluoro-[1,1';2',1'']terphenyl-2"-carboxylic acid;

35 2"-benzyloxy-5-fluoro-[1,1';2',1'']terphenyl-3-carboxylic acid;

4"-amino-2-benzyloxy-[1,1';2',1'']terphenyl-3"-carboxylic acid;

5"-acetylamino-2-benzyloxy-[1,1';2',1'']terphenyl-2"-carboxylic acid;

2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2"-carboxylic acid;

2-benzyloxy-[1,1';2',1'']terphenyl-3"-carboxylic acid;

40 2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2"-carboxylic acid amide;

5-(2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3"-yl)-1H-tetrazole;

N-[1-(2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2"-yl)-methanoyl]-benzenesulfonamide;

2-benzyloxy-[1,1';2',1'']terphenyl-4"-sulfonic acid (1-phenyl-methanoyl)-amide;

- 2-benzyloxy-[1,1';2',1'']terphenyl-4"-sulfonic acid [1-(4-nitro-phenyl)-methanoyl]-amide;  
 2-benzyloxy-[1,1';2',1'']terphenyl-3"-sulfonic acid acetyl-amide;  
 5-chloro-2-(3-methyl-butoxy)-[1,1';2',1'']terphenyl-3"-carboxylic acid;  
 5-chloro-2-(4-fluoro-benzyloxy) -[1,1';2',1'']terphenyl-3"-carboxylic acid;  
 5 5-chloro-2-(2,4-difluoro-benzyloxy) -[1,1';2',1''] terphenyl-3"-carboxylic acid;  
 5-chloro-2-(4-chloro-benzyloxy)-[1,1';2',1''] terphenyl-3"carboxylic acid;  
 5-chloro-2-(2-fluoro-4-chloro-benzyloxy) -[1,1';2',1''] terphenyl-3"carboxylic;  
 5-chloro-2-(4-isobutoxy)-[1,1';2',1''] terphenyl-3"-carboxylic acid;  
 5-chloro-2-(pyridin-2-ylmethoxy) -[1,1';2',1''] terphenyl-3"carboxylic acid;  
 10 5-chloro-2-(pyridin-4-ylmethoxy) -[1,1';2',1''] terphenyl-3"carboxylic acid;  
 5-chloro-2-(pyridin-3-ylmethoxy) -[1,1';2',1''] terphenyl-3"carboxylic acid;  
 5-chloro-2-cyclohexylmethoxy -[1,1';2',1'']terphenyl-3"carboxylic acid;  
 5-chloro-2-(thiophen-3-ylmethoxy) -[1,1';2',1''] terphenyl-3"carboxylic acid;  
 5-chloro-2-(thiophen-2-ylmethoxy) -[1,1';2',1''] terphenyl-3"carboxylic acid;  
 15 5-chloro-2-cyclopentylmethoxy -[1,1';2',1'']terphenyl-3"carboxylic acid;  
 5-chloro-2-propoxy -[1,1';2',1''] terphenyl-3"-carboxylic acid;  
 2-butoxy-5-chloro-[1,1';2',1''] terphenyl-3"-carboxylic acid;  
 5-chloro-2-isopropoxy -[1,1';2',1''] terphenyl-3"-carboxylic acid;  
 5-chloro-2-isobutoxy-[1,1';2',1'']terphenyl-2"-carboxylic acid;  
 20 and derivatives thereof.

Further examples of the invention include the compounds of Examples 44 to 90 and derivatives thereof.

- 25 Preferred examples include the compounds of Examples 52, 72, 73, 74, 75, 76, 85 and 88 and derivatives thereof.

Preferably compounds are selective for EP<sub>1</sub> over EP<sub>3</sub>. More preferably the compounds are 100 fold selective, more preferably 1000 fold selective for EP<sub>1</sub> over EP<sub>3</sub>.

30

Derivatives of the compounds of formula (I) include pharmaceutically acceptable derivatives.

The invention is described using the following definitions unless otherwise indicated.

- 35 The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I).
- 40 It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be pharmaceutically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the pharmaceutically acceptable salts thereof.

5

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acid.

Preferred examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pantoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

The terms "halogen or halo" are used to represent fluorine, chlorine, bromine or iodine, more preferably fluorine, chlorine and bromine.

The term "alkyl" as a group or part of a group means a straight, branched or cyclic chain alkyl group or combinations thereof. Unless hereinbefore defined, examples of alkyl include C<sub>1-8</sub>alkyl, for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopentyl or cyclohexyl or combinations thereof.

The term "alkoxy" as a group or as part of a group means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain. Unless hereinbefore defined examples of alkoxy include C<sub>1-8</sub>alkoxy, for example methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, sec-butoxy, iso-butoxy, tert-butoxy, pentoxy, hexyloxy, cyclopentoxy or cyclohexyloxy.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon to carbon double bond. C<sub>2-6</sub>alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "heterocyclyl" as a group or as part of a group means an aromatic or non-aromatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents, preferably one or two substituents. Examples of 5- membered heterocyclyl groups include furyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thiophenyl, pyrazolyl or tetrazolyl. Examples of 6-membered heterocyclyl groups are pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or tetrazinyl.

The term "bicyclic heterocyclyl" when used herein means a fused bicyclic aromatic or non-aromatic bicyclic heterocyclyl ring system comprising up to four, preferably one or two, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring. Examples of bicyclic heterocyclyl groups include quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzoxadiazolyl, benzthiadiazolyl, indolyl, benztriazolyl or naphthyridinyl.

The term "aryl" as a group or as part of a group means a 5- or 6- membered aromatic ring for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic, for example naphthyl. An aryl group may be substituted by up to four, preferably one to three substituents. Preferably the aryl group is phenyl.

The term "heteroaryl" as a group or as part of a group means a monocyclic five or six membered aromatic ring, or a fused bicyclic aromatic ring system comprising two of such monocyclic five or six membered aromatic rings. These heteroaryl rings contain one or more heteroatoms selected from nitrogen, oxygen or sulfur, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. A heteroaryl group may be optionally substituted by one or more substituents for example one or two substituents. Examples of "heteroaryl" used herein include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuryl, benzothiophenyl, indolyl, and indazolyl.

Optional substituents for alkyl or alkenyl groups unless hereinbefore defined include OH,  $\text{CO}_2\text{R}^4$ ,  $\text{NR}^4\text{R}^5$ , (O),  $-\text{OC}_{1-6}\text{alkyl}$  or halo e.g. Cl, Br or F, wherein  $\text{R}^4$ , and  $\text{R}^5$  are as hereinbefore defined for compounds of formula (I). An alkyl or alkenyl group may be substituted by one or  
5 more optional substituents, for example up to 5, 4, 3, or 2 optional substituents. Particular substituted alkyl groups include those substituted by one or more fluorine atoms e.g.  $\text{CH}_2\text{F}$ ,  $\text{CHF}_2$ ,  $\text{CF}_3$ ,  $\text{C}_2\text{F}_5$  etc, especially  $\text{CF}_3$ .

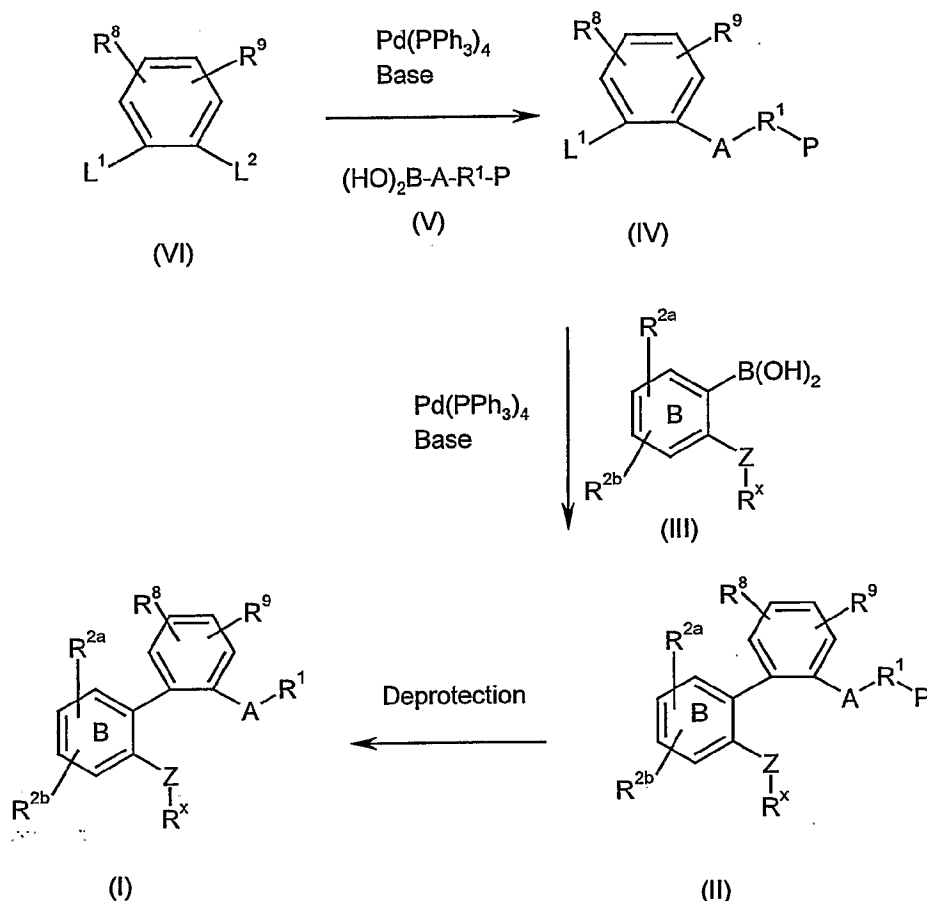
Optional substituents for alkoxy groups unless hereinbefore defined include OH, and halo e.g.  
10 Cl, Br or F. An alkoxy group may be substituted by one or more optional substituents, for example up to 5, 4, 3, or 2 optional substituents. Particular substituted alkoxy groups include those substituted by one or more fluorines e.g.  $\text{OCH}_2\text{F}$ ,  $\text{OCHF}_2$ ,  $\text{OCF}_3$ ,  $\text{OC}_2\text{F}_5$  etc.

Optional substituents for A, aryl, heteroaryl or heterocyclyl groups, unless hereinbefore defined,  
15 include one or two substituents selected from halogen; optionally substituted  $\text{C}_{1-6}\text{alkyl}$ ; optionally substituted  $\text{C}_{1-6}\text{alkoxy}$ ; optionally substituted  $\text{C}_{2-6}\text{alkenyl}$ ; optionally substituted  $\text{C}_{2-6}\text{alkynyl}$ ;  $\text{C}_{1-6}\text{haloalkyl}$ ;  $\text{C}_{1-6}\text{haloalkoxy}$ ;  $\text{NO}_2$ ; CN;  $\text{NR}^4\text{R}^5$ ;  $\text{CONR}^4\text{R}^5$ ;  $\text{SO}_2\text{NR}^4\text{R}^5$ ; optionally substituted  $\text{SO}_n\text{C}_{1-6}\text{alkyl}$ ; optionally substituted  $\text{NR}^5(\text{CO})\text{C}_{1-6}\text{alkyl}$ ;  $\text{NR}^5(\text{CO})\text{aryl}$  optionally substituted by one or two substituents selected from halo,  $\text{NR}^4\text{R}^5$ ,  $\text{C}_{1-6}\text{alkyl}$ , and  $\text{OC}_{1-6}\text{alkyl}$ ;  $\text{NR}^5(\text{CO})\text{heteroaryl}$   
20 optionally substituted by one or two substituents selected from halo,  $\text{NR}^4\text{R}^5$ ,  $\text{C}_{1-6}\text{alkyl}$ , and  $\text{OC}_{1-6}\text{alkyl}$ ; and optionally substituted  $\text{NR}^5(\text{SO}_2)\text{C}_{1-6}\text{alkyl}$ ; wherein n,  $\text{R}^4$  and  $\text{R}^5$  are as hereinbefore defined for compounds of formula (I).

Unless otherwise defined, certain optional substituents for A, aryl, heteroaryl or heterocyclyl  
25 groups include halogen;  $\text{C}_{1-6}\text{alkyl}$ ;  $\text{C}_{1-6}\text{alkoxy}$ ;  $\text{C}_{2-6}\text{alkenyl}$ ;  $\text{C}_{2-6}\text{alkynyl}$ ;  $\text{C}_{1-6}\text{haloalkyl}$ ;  $\text{C}_{1-6}\text{haloalkoxy}$ ;  $\text{NO}_2$ ; CN;  $\text{NR}^4\text{R}^5$ ;  $\text{CONR}^4\text{R}^5$ ;  $\text{SO}_2\text{NR}^4\text{R}^5$ ;  $\text{SO}_2\text{C}_{1-6}\text{alkyl}$ ;  $\text{NR}^5(\text{CO})\text{C}_{1-6}\text{alkyl}$ ;  $\text{NR}^5(\text{CO})\text{phenyl}$ ; and  $\text{NR}^5(\text{CO})\text{heteroaryl}$ ; wherein  $\text{R}^4$  and  $\text{R}^5$  are as hereinbefore defined for compounds of formula (I). Alternative optional substituents include halogen,  $\text{C}_{1-6}\text{alkyl}$ , and  $\text{C}_{1-6}\text{alkoxy}$ .

When the heteroatom nitrogen replaces a carbon atom in a  $\text{C}_{1-6}\text{alkyl}$  group, or when  
nitrogen is present in a heteroaryl, heterocyclyl or bicyclic heterocyclyl group the nitrogen  
atom will, where appropriate be substituted by one or two substituents selected from  
hydrogen and  $\text{C}_{1-6}\text{alkyl}$ , preferably hydrogen and  $\text{C}_{1-6}\text{alkyl}$ , more preferably hydrogen.  
35

Compounds of formula (I) can be prepared as set forth in the following scheme and in the  
examples. The following processes form another aspect of the present invention.



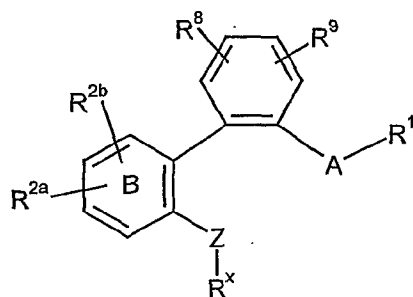
wherein  $L^1$  and  $L^2$  are each a leaving group for example halo, e.g. bromo; P is an optional protecting group for example methyl, ethyl or benzyl esters; and A, B,  $R^{2a}$ ,  $R^{2b}$ , Z,  $R^8$ ,  $R^9$ ,  $R^1$  and  $R^x$  are as defined for compounds of formula (I).

The skilled person will recognise when the use of a protecting group is necessary.

Suitable reaction conditions for the deprotection of a compound of formula (II) include heating in ethanolic sodium hydroxide solution.

Suitable reaction conditions for the reaction of a compound of formula (VI) with a boronic acid of formula (V), or a compound of formula (IV) with a boronic acid of formula (III) include heating with tetrakis(triphenylphosphine)palladium (0) and an inorganic base, for example potassium carbonate or silver carbonate, in a solvent, e.g. ethylene glycol dimethyl ether (DME), toluene and ethanol, preferably in a ratio of 1:1.

Accordingly the present invention also provides a process for the preparation of a compound of formula (I) or a derivative thereof:



(I)

wherein:

A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

5 B represents a phenyl or pyridyl ring;

Z represents O, S, SO, or SO<sub>2</sub>;

R<sup>1</sup> represents CO<sub>2</sub>R<sup>4</sup>, CN, CONR<sup>5</sup>R<sup>6</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>4</sup>, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO<sub>2</sub>alkyl, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>CONR<sup>5</sup>R<sup>6</sup>, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

10

R<sup>2a</sup> and R<sup>2b</sup> independently represents hydrogen, halogen, optionally substituted alkyl, optionally substituted alkoxy, CN, SO<sub>2</sub>alkyl, SR<sup>5</sup>, NO<sub>2</sub>, optionally substituted aryl, CONR<sup>5</sup>R<sup>6</sup> or optionally substituted heteroaryl;

R<sup>x</sup> represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR<sup>4</sup>, O and SO<sub>n</sub>, wherein n is 0, 1 or 2; or R<sup>x</sup> represents optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocyclyl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-bicyclic heterocyclyl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-aryl;

15

R<sup>4</sup> represents hydrogen or an optionally substituted alkyl;

R<sup>5</sup> represents hydrogen or an optionally substituted alkyl;

20 R<sup>6</sup> represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO<sub>2</sub>aryl, optionally substituted SO<sub>2</sub>alkyl, optionally substituted SO<sub>2</sub>heteroaryl, CN, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>aryl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>heteroaryl or COR<sup>7</sup>;

R<sup>7</sup> represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

25

R<sup>8</sup> and R<sup>9</sup> independently represent hydrogen, chloro, fluoro, CF<sub>3</sub>, C<sub>1-3</sub>alkoxy or C<sub>1-3</sub>alkyl;

Q<sup>a</sup> and Q<sup>b</sup> are independently selected from hydrogen and CH<sub>3</sub>;

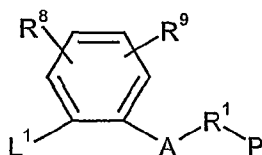
wherein when A is a 6-membered ring the R<sup>1</sup> substituent and phenyl ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R<sup>1</sup> substituent and phenyl ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;

30

comprising:

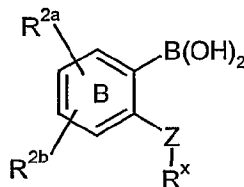
reacting a compound of formula (IV):





(IV)

wherein  $R^8$ ,  $R^9$ , A, and  $R^1$  are as hereinbefore defined above for a compound of formula (I),  $L^1$  is a leaving group and P is an optional protecting group;  
with a compound of formula (III):



(III)

wherein  $R^{2a}$ ,  $R^{2b}$ , B, Z, and  $R^x$  are as hereinbefore defined above for a compound of formula (I);

and where required, and in any order converting:

one group A to another group A, and/or

one group  $R^x$  to another group  $R^x$ ;

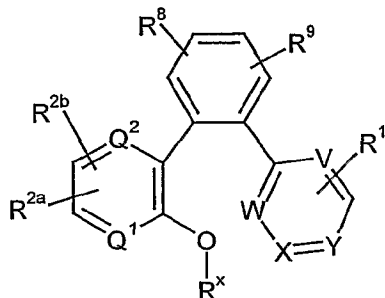
and where required carrying out the following optional steps in any order:

effecting deprotection; and/or

converting one group  $R^1$  to another group  $R^1$ ; and/or

forming a derivative of the compound of formula (I) so formed.

The present invention also provides a process for the preparation of a compound of formula (Ia) or a derivative thereof:



(Ia)

W, X, and Y each represents  $CR^{12}$  or N;

V represents  $CR^1$ ,  $CR^{12}$  or N;

wherein at least two of W, X, Y or V is  $CR^{12}$ ; and  $R^{12}$  is independently selected from hydrogen, halogen, CN, optionally substituted  $CO_2C_{1-6}alkyl$ ,  $CONR^5R^6$ ,  $NR^5R^6$ , optionally substituted  $NR^5COC_{1-6}alkyl$ , optionally substituted  $NR^5Cophenyl$ , optionally substituted  $NR^5COpiperidiny$ , optionally substituted  $NR^5COheterocycl$ , optionally substituted  $NR^5SO_2C_{1-6}alkyl$ , OH, optionally substituted  $OC_{1-6}alkyl$ , optionally substituted  $C_{1-6}alkyl$  and  $NR^{10}R^{11}$ ;

$Q^1$  and  $Q^2$  each represents CH, or one of  $Q^1$  and  $Q^2$  is N and the other is CH;  
 $R^1$  is  $CO_2H$ , optionally substituted  $CONHSO_2$ aryl,  $CH_2CO_2H$ ,  $SO_2NHCOR^7$ ,  $SO_2NHCOC_{1-6}$ alkyl or tetrazolyl and is positioned 1,2-, or 1,3- relative to the phenyl ring;  
 $R^{2a}$  and  $R^{2b}$  are independently selected from hydrogen, halo, or  $CF_3$ ;

5  $R^x$  represents optionally substituted  $C_{1-6}$ alkyl, or  $R^x$  represents optionally substituted  $CQ^aQ^b$ -heterocyclyl or optionally substituted  $CQ^aQ^b$ -phenyl wherein  $Q^a$  and  $Q^b$  are independently selected from hydrogen and  $CH_3$ ;

$R^4$  represents hydrogen or an optionally substituted  $C_{1-6}$ alkyl;

$R^5$  represents hydrogen or an optionally substituted  $C_{1-6}$ alkyl;

10  $R^6$  represents hydrogen or an optionally substituted  $C_{1-6}$ alkyl, optionally substituted  $SO_2$ phenyl, optionally substituted  $SO_2$ heterocyclyl group, CN, optionally substituted  $CH_2$ phenyl or  $COR^7$ ;

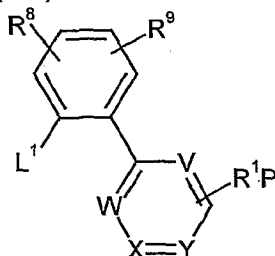
$R^7$  represents hydrogen, optionally substituted heteroaryl or optionally substituted phenyl;

$R^8$  and  $R^9$  independently represent hydrogen, chloro, fluoro,  $CF_3$ ,  $C_{1-3}$ alkoxy or  $C_{1-3}$ alkyl;

15 and

$R^{10}$  and  $R^{11}$  together with the nitrogen atom to which they are attached form a morpholine ring, a 5- or 6-membered lactam ring or a 5- or 6-membered cyclic sulphonamide, comprising:

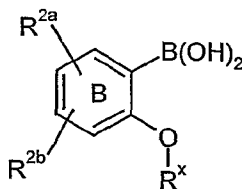
reacting a compound of formula (IVa):



(IVa)

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wherein  $R^8$ ,  $R^9$ , X, Y, V and  $R^1$  are as hereinbefore defined above for a compound of formula (I),  $L^1$  is a leaving group and P is an optional protecting group;  
 with a compound of formula (IIIa):



(IIIa)

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wherein  $R^{2a}$ ,  $R^{2b}$ , B, and  $R^x$  are as hereinbefore defined above for a compound of formula (I);

and where required, and in any order converting:

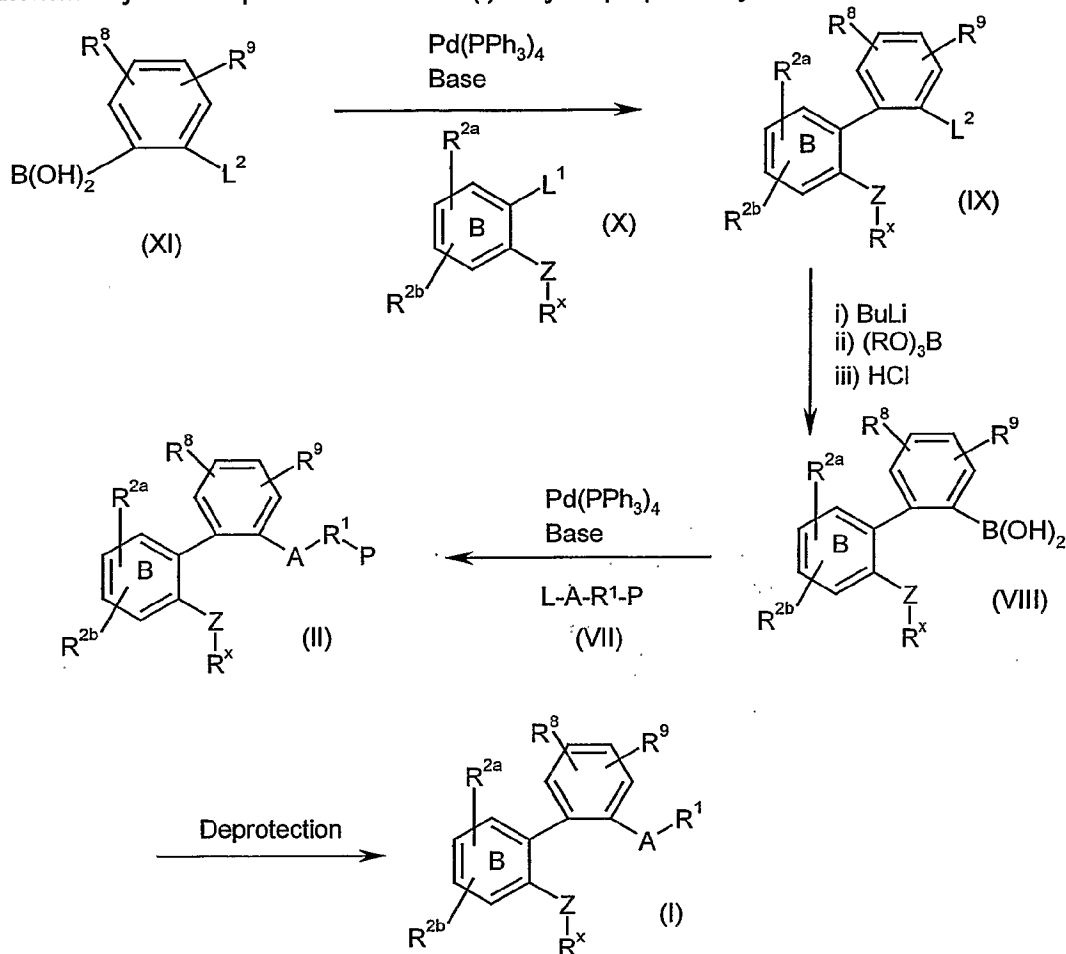
one group  $R^{12}$  to another group  $R^{12}$ , and/or

30 one group  $R^x$  to another group  $R^x$ ;

and where required carrying out the following optional steps in any order:  
 effecting deprotection; and/or  
 converting one group  $R^1$  to another group  $R^1$ ; and/or  
 forming a derivative of the compound of formula (I) so formed.

5

Alternatively the compounds of formula (I) may be prepared by the route described below:



wherein L,  $L^1$  and  $L^2$  are each a leaving group for example halo, e.g. bromo; P is an optional protecting group, R is  $C_{1-4}$  alkyl e.g. methyl or isopropyl, and A, B,  $R^{2a}$ ,  $R^{2b}$ , Z,  $R^8$ ,  $R^9$ ,  $R^1$  and  $R^x$  are as defined for compounds of formula (I).

10

When  $R^1$  is  $CO_2H$  examples of protecting groups include  $C_{1-4}$ alkyl, e.g. methyl, ethyl, or benzyl esters.

15

Suitable reaction conditions for the deprotection of a compound of formula (II) include heating in ethanolic sodium hydroxide solution.

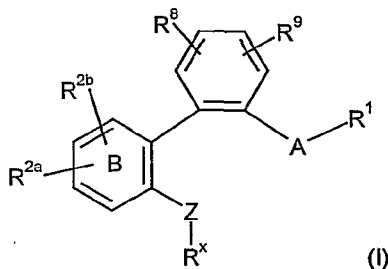
Suitable reaction conditions for the reaction of a compound of formula (X) with a boronic acid of formula (XI), or a compound of formula (VII) with a boronic acid of formula (VIII) include heating with tetrakis(triphenylphosphine)palladium (0) and an inorganic base, for

20

example potassium carbonate or silver carbonate, in a solvent, e.g. ethylene glycol dimethyl ether (DME), toluene and ethanol, preferably in a ratio of 1:1.

- Suitable reaction conditions for the conversion of a compound of formula (IX) to a compound of formula (VIII) include reacting the compound of formula (IX) wherein  $L^2$  is Br or I with butyl lithium (BuLi) or iso-propyl magnesium chloride in a solvent such as diethyl ether or tetrahydrofuran, treating with trimethyl borate and subsequent acidification.

- Accordingly the present invention also provides a process for the preparation of a compound of formula (I) or a derivative thereof:



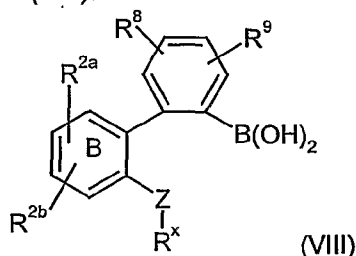
wherein:

- A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;
- B represents a phenyl or pyridyl ring;
- Z represents O, S, SO, or SO<sub>2</sub>;
- R<sup>1</sup> represents CO<sub>2</sub>R<sup>4</sup>, CN, CONR<sup>5</sup>R<sup>6</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>4</sup>, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO<sub>2</sub>alkyl, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>CONR<sup>5</sup>R<sup>6</sup>, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;
- R<sup>2a</sup> and R<sup>2b</sup> independently represents hydrogen, halogen, optionally substituted alkyl, optionally substituted alkoxy, CN, SO<sub>2</sub>alkyl, SR<sup>5</sup>, NO<sub>2</sub>, optionally substituted aryl, CONR<sup>5</sup>R<sup>6</sup> or optionally substituted heteroaryl;
- R<sup>x</sup> represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR<sup>4</sup>, O and SO<sub>n</sub>, wherein n is 0, 1 or 2; or R<sup>x</sup> represents optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocyclyl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-bicyclic heterocyclyl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-aryl;
- R<sup>4</sup> represents hydrogen or an optionally substituted alkyl;
- R<sup>5</sup> represents hydrogen or an optionally substituted alkyl;
- R<sup>6</sup> represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO<sub>2</sub>aryl, optionally substituted SO<sub>2</sub>alkyl, optionally substituted SO<sub>2</sub>heteroaryl, CN, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>aryl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>heteroaryl or COR<sup>7</sup>;
- R<sup>7</sup> represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;
- R<sup>8</sup> and R<sup>9</sup> independently represent hydrogen, chloro, fluoro, CF<sub>3</sub>, C<sub>1-3</sub>alkoxy or C<sub>1-3</sub>alkyl;
- Q<sup>a</sup> and Q<sup>b</sup> are independently selected from hydrogen and CH<sub>3</sub>;

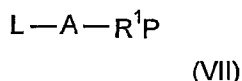
wherein when A is a 6-membered ring the R<sup>1</sup> substituent and phenyl ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R<sup>1</sup> substituent and phenyl ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;

5 comprising:

reacting a compound of formula (VIII):



wherein B, R<sup>2a</sup>, R<sup>2b</sup>, Z, R<sup>8</sup>, R<sup>9</sup>, and R<sup>x</sup> are as defined for compounds of formula (I), with a compound of formula (VII):



10

wherein A and R<sup>1</sup> are as hereinbefore defined for compounds of formula (I), L is a leaving group and P is an optional protecting group;

and where required, and in any order, converting:

one group A to another group A, and/or

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one group R<sup>x</sup> to another group R<sup>x</sup>;

and where required carrying out the following optional steps in any order:

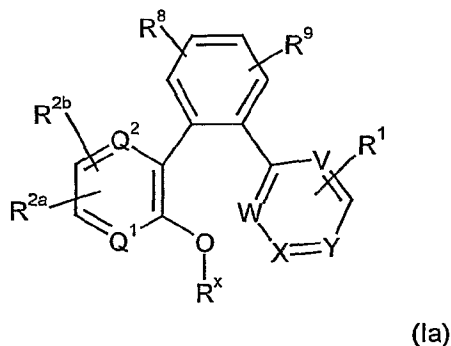
effecting deprotection; and/or

converting one group R<sup>1</sup> to another group R<sup>1</sup>; and/or

forming a derivative of the compound of formula (I) so formed.

20

The present invention also provides a process for the preparation of a compound of formula (Ia) or a derivative thereof:



25

W, X, and Y each represents CR<sup>12</sup> or N;

V represents CR<sup>1</sup>, CR<sup>12</sup> or N;

wherein at least two of W, X, Y or V is CR<sup>12</sup>; and R<sup>12</sup> is independently selected from hydrogen, halogen, CN, optionally substituted CO<sub>2</sub>C<sub>1-6</sub>alkyl, CONR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>R<sup>6</sup>, optionally substituted NR<sup>5</sup>COC<sub>1-6</sub>alkyl, optionally substituted NR<sup>5</sup>COPhenyl, optionally substituted

NR<sup>5</sup>COpiperidinyl, optionally substituted NR<sup>5</sup>COheterocyclyl, optionally substituted NR<sup>5</sup>SO<sub>2</sub>C<sub>1-6</sub>alkyl, OH, optionally substituted OC<sub>1-6</sub>alkyl, optionally substituted C<sub>1-6</sub>alkyl and NR<sup>10</sup>R<sup>11</sup>;

Q<sup>1</sup> and Q<sup>2</sup> each represents CH, or one of Q<sup>1</sup> and Q<sup>2</sup> is N and the other is CH;

R<sup>1</sup> is CO<sub>2</sub>H, optionally substituted CONHSO<sub>2</sub>aryl, CH<sub>2</sub>CO<sub>2</sub>H, SO<sub>2</sub>NHCOR<sup>7</sup>, SO<sub>2</sub>NHCOC<sub>1-</sub>

5 <sub>6</sub>alkyl or tetrazolyl and is positioned 1,2-, or 1,3- relative to the phenyl ring;

R<sup>2a</sup> and R<sup>2b</sup> are independently selected from hydrogen, halo, or CF<sub>3</sub>;

R<sup>x</sup> represents optionally substituted C<sub>1-8</sub>alkyl, or R<sup>x</sup> represents optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocyclyl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-phenyl wherein Q<sup>a</sup> and Q<sup>b</sup> are independently selected from hydrogen and CH<sub>3</sub>;

10 R<sup>4</sup> represents hydrogen or an optionally substituted C<sub>1-6</sub>alkyl;

R<sup>5</sup> represents hydrogen or an optionally substituted C<sub>1-6</sub>alkyl;

R<sup>6</sup> represents hydrogen or an optionally substituted C<sub>1-6</sub>alkyl, optionally substituted SO<sub>2</sub>phenyl, optionally substituted SO<sub>2</sub>heterocyclyl group, CN, optionally substituted CH<sub>2</sub>phenyl or COR<sup>7</sup>;

15 R<sup>7</sup> represents hydrogen, optionally substituted heteroaryl or optionally substituted phenyl;

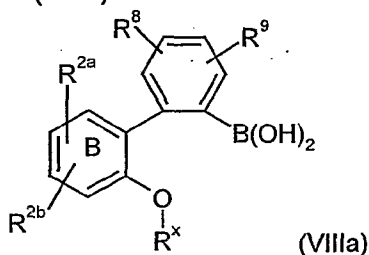
R<sup>8</sup> and R<sup>9</sup> independently represent hydrogen, chloro, fluoro, CF<sub>3</sub>, C<sub>1-3</sub>alkoxy or C<sub>1-3</sub>alkyl;

and

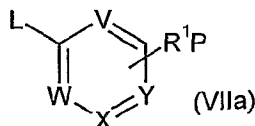
R<sup>10</sup> and R<sup>11</sup> together with the nitrogen atom to which they are attached form a morpholine ring, a 5- or 6-membered lactam ring or a 5- or 6-membered cyclic sulphonamide,

20 comprising:

reacting a compound of formula (VIIIa):



wherein B, R<sup>2a</sup>, R<sup>2b</sup>, R<sup>8</sup>, R<sup>9</sup>, and R<sup>x</sup> are as defined for compounds of formula (Ia), with a compound of formula (VIIa):



25

wherein V, W, X, Y and R<sup>1</sup> are as hereinbefore defined for compounds of formula (I), L is a leaving group and P is an optional protecting group;

and where required, and in any order, converting:

one group R<sup>12</sup> to another group R<sup>12</sup>; and/or

30 one group R<sup>x</sup> to another group R<sup>x</sup>;

and where required carrying out the following optional steps in any order:

effecting deprotection; and/or

converting one group R<sup>1</sup> to another group R<sup>1</sup>; and/or

forming a derivative of the compound of formula (I) so formed.

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It will be appreciated that certain substituents in intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art.

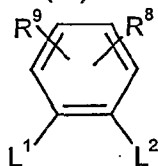
- 5 A group  $R^1$  may be converted to another group  $R^1$  by use of conventional organic transformations known to those skilled in the art. For example  $R^1 = CO_2H$  may be converted to an amide, e.g.  $CONHCQ^aQ^b$ aryl or  $CONHCQ^aQ^b$ heteroaryl wherein  $Q^a$  and  $Q^b$  are selected from hydrogen and  $CH_3$ , by conventional methods for the preparation of amides as described in, for example, Richard Larock, *Comprehensive Organic*  
10 *Transformations*, 2nd edition, Wiley-VCH, ISBN 0-471-19031-4.

- Certain substituents in any of the reaction intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art. Examples of substituents which may be converted include one group  $R^x$  to another  
15 group  $R^x$ ; and one substituent on a group A to another substituent on a group A. Examples of such transformations include the reduction of a nitro group to give an amino group; alkylation and amidation of amino groups; hydrolysis of esters, alkylation of hydroxy and amino groups; and amidation and esterification of carboxylic acids. Such transformations are well known to those skilled in the art and are described in for example,  
20 Richard Larock, *Comprehensive Organic Transformations*, 2nd edition, Wiley-VCH, ISBN 0-471-19031-4.

- For example, when  $R^x$  is p-methoxybenzyl, cleavage of the ether to give the phenol or pyridinol is carried out using, for example, using acid e.g. HCl/dioxane or HBr/acetic acid  
25 or using sodium methanethiolate. When  $R^x$  is methyl, cleavage of the ether to give the phenol is carried out using, for example, sodium methanethiolate. Cleavage of the ether to give a pyridinol is carried out in the presence of, for example, trifluoroacetic acid. Conversion to another  $R^x$  group, for example a substituted benzyl group, may be effected by reaction of the phenol or pyridinol with a suitable substituted benzyl bromide. The  
30 skilled person will appreciate that conversion of the protecting group P to another protecting group P may also occur under the reaction conditions used. When  $R^x$  is benzyl, cleavage of the ether to give the phenol or pyridinol may be carried out by hydrogenation according to known methods e.g.  $H_2$ -Pd/C or  $NH_4CO_2H$ -Pd/C. The resulting phenol or pyridinol can then be converted to another group  $R^x$  as described above.

- 35 It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. The skilled person will recognise when a protecting group is required. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic  
40 synthesis', New York, Wiley (1981), can be used. For example, carboxylic acid groups can be protected as esters. Deprotection of such groups is achieved using conventional procedures known in the art. It will be appreciated that protecting groups may be interconverted by conventional means.

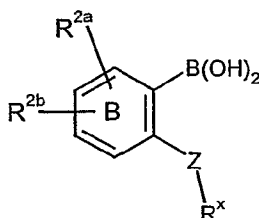
Phenyl intermediates of the formula (VI):



(VI)

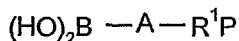
- wherein  $L^1$ ,  $L^2$  are as defined above, and  $R^8$  and  $R^9$  are as hereinbefore defined for compounds of formula (I) are commercially available or may be readily prepared according to known methods.

Compounds of the formula (III):



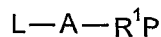
- wherein  $L^4$  is as hereinbefore defined,  $R^{2a}$ ,  $R^{2b}$ ,  $Z$ ,  $B$  and  $R^x$  and are as defined for compounds of formula (I) are commercially available, or may readily be prepared by methods known to those skilled in the art, for example from suitable commercially available pyridinols, anisoles or phenols or compounds of formula (X) using methods as described in the examples.

Intermediates of the formula (V):



- wherein  $P$  is an optional protecting group and  $R^1$  and  $A$  are as hereinbefore defined for compounds of formula (I) are commercially available or may readily be prepared, for example, from suitable halobenzoic acid esters according to known methods, for example using methods as described in the examples.

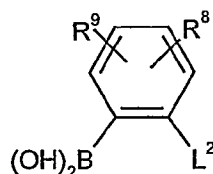
Intermediates of the formula (VII):



- herein  $L$  is a leaving group, e.g.  $Br$ ,  $P$  is an optional protecting group and  $R^1$  and  $A$  are as hereinbefore defined for compounds of formula (I) are commercially available or may readily be prepared according to known methods, for example using methods as described in the examples.

- Phenyl intermediates of the formula (XI):

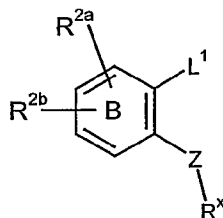




wherein  $L^2$  is a leaving group, and  $R^8$  and  $R^9$  are as hereinbefore defined for compounds of formula (I) are commercially available or may be readily prepared according to known methods from the corresponding compound of formula (VI).

5

Compounds of the formula (X):



wherein  $L^1$  is leaving group,  $R^{2a}$ ,  $R^{2b}$ ,  $Z$ ,  $B$  and  $R^x$  and are as defined for compounds of formula (I) are commercially available, or may readily be prepared by methods known to those skilled in the art, for example from suitable commercially available pyridinols, anisoles or phenols using methods as described in the examples.

10

The preparation and reactions of boronic acids of formula (III), formula (V), formula (VIII) and (XI) is reviewed in Suzuki *et al*, *Synth. Commun.*, 1981, 11, 513; Martin *et al*, *Acta. Chim. Scand.*, 1993, 47, 221; and Miyaura *et al*, *Chem. Rev.*, 1995, 95, 2457. For example, 2-benzyloxy-5-chlorophenylboronic acid may be prepared from 2-benzyloxy-5-chloro-iodobenzene. 2-Benzyloxy-5-chloro-iodobenzene may be prepared from 4-chloro-2-iodoanisole by demethylation followed by benzylation according to known methods.

15

It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

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The compounds of the invention bind to the  $EP_1$  receptor and they are therefore considered to be useful in treating conditions mediated by the action of  $PGE_2$  at  $EP_1$  receptors.

Conditions mediated by the action of  $PGE_2$  at  $EP_1$  receptors include pain; fever; inflammation; immunological diseases; abnormal platelet function diseases; impotence or erectile dysfunction; bone disease; hemodynamic side effects of non-steroidal anti-

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inflammatory drugs; cardiovascular diseases; neurodegenerative diseases and neurodegeneration; neurodegeneration following trauma; tinnitus; dependence on a dependence-inducing agent; complications of Type I diabetes; and kidney dysfunction.

- 5 The compounds of formula (I) are considered to be useful as analgesics. They are therefore considered useful in the treatment or prevention of pain.

10 The compounds of formula (I) are considered useful as analgesics to treat acute pain, chronic pain, neuropathic pain, inflammatory pain, visceral pain, pain associated with cancer and fibromyalgia, pain associated with migraine, tension headache and cluster headaches, and pain associated with functional bowel disorders, non-cardiac chest pain and non-ulcer dyspepsia.

15 The compounds of formula (I) are considered useful in the treatment of chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other  
20 viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

25 The compounds of the invention are considered to be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified  
30 according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to  
35 have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful  
40 sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) are also considered useful in the treatment of fever.

5 The compounds of formula (I) are also considered useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract  
10 disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthesia gravis, multiple  
15 sclerosis, sarcoidosis, nephrotic syndrome, Bechet's syndrome, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

20 The compounds of formula (I) are also considered useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

25 The compounds of formula (I) are also considered useful in the treatment of diseases relating to abnormal platelet function (e.g. occlusive vascular diseases).

The compounds of formula (I) are also considered useful for the preparation of a drug with diuretic action.

30 The compounds of formula (I) are also considered useful in the treatment of impotence or erectile dysfunction.

35 The compounds of formula (I) are also considered useful in the treatment of bone disease characterised by abnormal bone metabolism or resorption such as osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculus, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing  
40 spondylitis, tendinitis and bursitis.

The compounds of formula (I) are also considered useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

The compounds of formula (I) are also considered useful in the treatment of cardiovascular diseases such as hypertension or myocardiac ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

The compounds of formula (I) are also considered useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

The compounds of formula (I) are also considered useful in the treatment of neuroprotection and in the treatment of neurodegeneration following trauma such as stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) are also considered useful in the treatment of tinnitus.

The compounds of formula (I) are also considered useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

The compounds of formula (I) are also considered useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

The compounds of formula (I) are also considered useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors.

5

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

10

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

15

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors.

20

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder.

25

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

30

Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

35

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

40

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

- 5 For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously).

- 10 The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

- 15 Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

- 20 The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

- 25 The EP<sub>1</sub> receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel  
30 blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; 5HT<sub>1</sub> agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or  
35 rizatriptan; EP<sub>4</sub> receptor ligands; EP<sub>2</sub> receptor ligands; EP<sub>3</sub> receptor ligands; EP<sub>4</sub> antagonists; EP<sub>2</sub> antagonists and EP<sub>3</sub> antagonists; cannabinoid receptor ligands; bradykinin receptor ligands and vanilloid receptor ligand. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

40

Additional COX-2 inhibitors are disclosed in US 5,474,995 US 5,633,272; US 5,466,823, US 6,310,099 and US 6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484,

WO 97/14691, WO 99/12930, WO 00/26216, WO 00/52008, WO 00/38311, WO 01/58881 and WO 02/18374.

5 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

10 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

15 When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

20 A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable derivatives for the treatment of man is from 0.01 to 30 mg/kg body weight per day and more particularly 0.1 to 10 mg/kg body weight per day, calculated as the free base, which may be administered as a single or divided dose, for example one to four times per day. The dose range for adult human beings is generally from 8 to 2000 mg/day, such as from 25 20 to 1000 mg/day, preferably 35 to 200 mg/day, calculated as the free base.

30 The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

35 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

40 The following non-limiting Examples illustrate the preparation of pharmacologically active compounds of the invention.

**EXAMPLES****Abbreviations:**

Bn (benzyl), Bu, Pr, Me, Et (butyl, propyl, methyl ethyl), DMSO (dimethyl sulfoxide), DCM  
 5 (dichloromethane), DME (ethylene glycol dimethyl ether), DMF (N,N-dimethylformamide),  
 EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), EtOAc (ethyl acetate), EtOH  
 (ethanol), HPLC (High pressure liquid chromatography), LCMS (Liquid  
 chromatography/Mass spectroscopy), MDAP (Mass Directed Purification), MeOH  
 (methanol), NMR (Nuclear Magnetic Resonance (spectrum)), Ph (phenyl), pTSA (para-  
 10 toluene sulphonic acid), SPE (Solid Phase Extraction), TBAF (tetrabutylammonium  
 fluoride), THF (tetrahydrofuran), s, d, t, q, m, br (singlet, doublet, triplet, quartet, multiplet,  
 broad.)

**LCMS**

15

- Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS
- Flow Rate: 3ml/min
- Injection Volume: 5µl
- Temp: RT

20

- UV Detection Range: 215 to 330nm

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.  
 B: 95% Acetonitrile + 0.05% Formic Acid.

Gradient: Time	A%	B%
0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

**Mass Directed Autopreparation**

25

Hardware:

Waters 600 gradient pump

Waters 2767 inject/collector

Waters Reagent Manager

30 Micromass ZMD mass spectrometer

Gilson Aspec - waste collector

Gilson 115 post-fraction UV detector

Software :

Micromass Masslynx version 4.0

35

Column



The column used is typically a Supelco LCABZ++ column whose dimensions are 20mm internal diameter by 100mm in length. The stationary phase particle size is 5µm.

Solvents:

A.: Aqueous solvent = Water + 0.1% Formic Acid

5 B: Organic solvent = MeCN: Water 95:5 +0.05% Formic Acid

Make up solvent = MeOH: Water 80:20 +50mMol Ammonium Acetate

Needle rinse solvent = MeOH: Water: DMSO 80:10:10

The method used depends on the analytical retention time of the compound of interest.

10 15-minute runtime, which comprises a 10-minute gradient followed by a 5-minute column flush and re-equilibration step.

MDP 1.5-2.2 = 0-30%B

MDP 2.0-2.8 = 5-30% B

MDP 2.5-3.0 = 15-55%B

15 MDP 2.8-4.0 = 30-80% B

MDP 3.8-5.5 = 50-90% B

Flow rate:

flow rate 20ml/min.

20

**Example 1: 2-Benzoyloxy-5-chloro-[1,1';2',1'']terphenyl-3"-carboxylic acid**

a) 2'-Bromo-biphenyl-3-carboxylic acid ethyl ester

A mixture of 1,2-dibromobenzene (0.63ml, 5.2mmol), (3-ethoxycarbonylphenyl)boronic acid (506mg, 2.6mmol), tetrakis(triphenylphosphine)palladium(0) (640mg, 0.6mmol) and  
25 potassium carbonate (2.879g, 20.9mmol) was heated in toluene-ethanol (1:1, 10ml at 90°C for 3 hours. Upon cooling, the mixture was diluted with ethyl acetate and water. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was  
30 purified by chromatography using Biotage with iso-hexane containing a gradient of DCM (2-15%) to yield the title compound (538mg, 34%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.40 (3H, t, J=7Hz), 4.40 (2H, q, J=7Hz), 7.20-7.25 (1H, m), 7.30-7.40 (2H, m), 7.50 (1H, t, J=8Hz), 7.62 (1H, br d, J=7Hz), 7.68 (1H, d, J=8Hz), 8.05-8.10 (2H, m). R<sub>f</sub> 0.31 (5% EtOAc in iso-hexane).

35

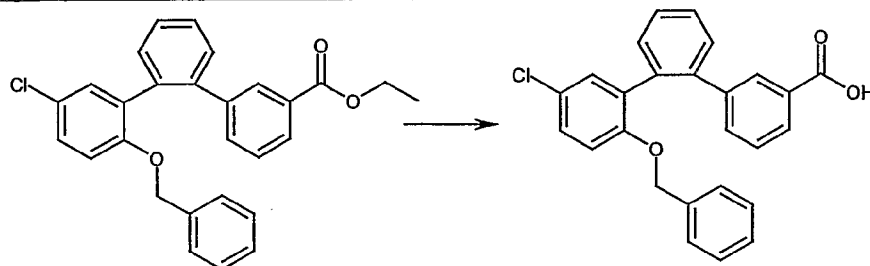
b) 2-Benzoyloxy-5-chloro-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester

2'-Bromo-biphenyl-3-carboxylic acid ethyl ester (157mg, 0.5mmol), 2-benzoyloxy-5-chloro-phenylboronic acid (157mg, 0.6mmol), tetrakis(triphenylphosphine)palladium(0) (66mg, 0.06mmol) and potassium carbonate (568mg, 4.1mmol) was heated in toluene-ethanol  
40 (1:1, 5ml) at 90°C for 4.5 hours. Upon cooling, the mixture was diluted with ethyl acetate and water. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The

residue was purified by chromatography using Biotage with iso-hexane containing a gradient of ethyl acetate (1-5%) to yield the title compound (105mg, 46%) as a white solid.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (3H, t, J=7Hz), 4.28 (2H, q, J=7Hz), 4.50-4.80 (2H, br. s), 6.60 (1H, d, J=9Hz), 6.94-6.98 (2H, m), 7.10 (1H, dd, J=3Hz, J=9Hz), 7.18-7.25 (6H, m's excess), 7.35-7.50 (4H, m), 7.83 (1H, s), 7.88 (1H, dt, J=1Hz, J=7.5Hz).  
 R<sub>f</sub> 0.15 (5% EtOAc in iso-hexane). LC/MS t = 4.23 (100%), [MH<sup>+</sup>] 443.

**c) 2-Benzyloxy-5-chloro-[1,1':2,1'']terphenyl-3"-carboxylic acid**



- 2-Benzyloxy-5-chloro-[1,1':2,1'']terphenyl-3"-carboxylic acid ethyl ester (103mg, 0.2mmol) was heated at 90°C in ethanol (2ml) containing 2M sodium hydroxide (1ml) in a reacti-vial for 2 hrs. The mixture was cooled to room temperature, diluted with ethyl acetate and washed with 2M HCl, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to yield the title compound (82mg, 85%).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.52-4.82 (2H, br. s), 6.62 (1H, d, J=9Hz), 6.99 (2H, m), 7.12 (1H, dd, J=3Hz, J=8.5Hz), 7.18-7.30 (6H, m's excess), 7.36-7.50 (4H, m), 7.90-7.95 (2H, m).  
 LC/MS t = 3.97 (100%), [MH<sup>-</sup>] 413, 415.

**Example 2: (2-Benzyloxy-5-chloro-[1,1':2,1'']terphenyl-3"-yl)-acetic acid**

- a) 1-(2'-Bromo-biphenyl-3-yl)-ethanone  
 A mixture of 3-acetylphenylboronic acid (1.64 g, 10mmol), 1,2-dibromobenzene (4.72g, 20 mmol), potassium carbonate (6.9 g, 50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.58 g, 0.5 mmol) in 1:1 toluene/ethanol (40 ml) was stirred and heated at 90°C under nitrogen for 16 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was purified by chromatography using Biotage with iso-hexane containing a gradient of dichloromethane (20-50%) to yield the title compound as a white solid (1.74 g 63%).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.64 (3H, s), 7.24-7.39 (3H, m), 7.52-7.70 (3H, m), 7.98-8.00 (2H, m).  
 LC/MS t=3.42, [MH<sup>+</sup>] 276.9.

**b) (2'-Bromophenyl-3-yl)-acetic acid methyl ester**

- Iodine (533 mg, 2.1 mmol) was added to a stirred suspension of 1-(2'-bromo-biphenyl-3-yl)-ethanone (550 mg, 2 mmol) and silver nitrate (714 mg, 4.2 mmol) in methanol (9 ml) and trimethyl orthoformate (3 ml) and the resulting mixture refluxed for 16 hours. After cooling the mixture was filtered, diluted with water and diethyl ether and the organic phase

dried ( $\text{MgSO}_4$ ) and evaporated to dryness. The residue was purified using Biotage with dichloromethane/iso-hexane (3:7) to yield the title compound as a colourless gum (499 mg 82%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.69 (2H, s), 3.71 (3H, s), 7.19-7.39 (7H, s), 7.66 (1H, d,  $J=8\text{Hz}$ ).

5 LC/MS  $t=3.49$ ,  $[\text{MH}^+]$  306.9.

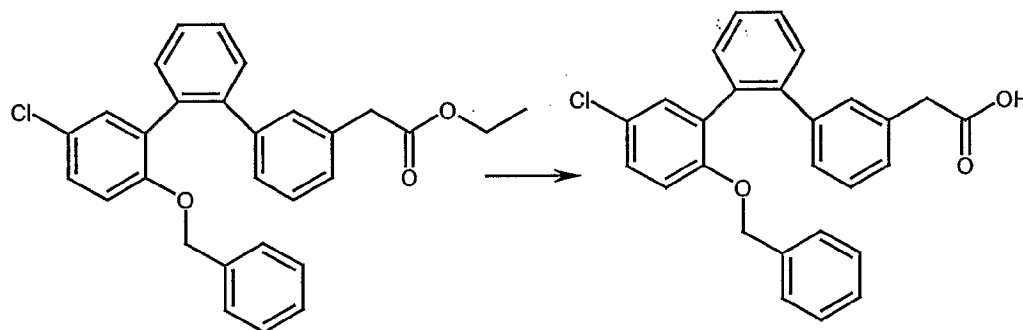
c) (2-Benzyloxy-5-chloro[1,1';2',1'']terphenyl-3''-yl)acetic acid ethyl ester

A mixture of (2'-bromo-biphenyl-3-yl)-acetic acid methyl ester (76 mg, 0.25 mmol), 2-benzyloxy-5-chloro-phenyl-boronic acid (72 mg, 0.275 mmol), potassium carbonate (276 mg, 2 mmol) and tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmol) in 1:1  
10 toluene/ethanol (3 ml) was heated and stirred at  $90^\circ\text{C}$  under nitrogen for 2 hours. After cooling the mixture was diluted with water and diethyl ether and the organic phase dried ( $\text{MgSO}_4$ ) and evaporated to dryness. The residue was purified by chromatography using Biotage with ethyl acetate/iso-hexane (1:19) to yield the title compound as a colourless  
15 gum (112 mg, 98%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.2 (3H, t,  $J=7\text{Hz}$ ), 3.40 (2H, s), 4.06 (2H, q,  $J=7\text{Hz}$ ), 4.66 (2H, br s), 6.59 (1H, d,  $J=8\text{Hz}$ ), 6.96-7.42 (15H, m).

d) (2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3''-yl)-acetic acid

20



A solution of (2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3''-yl)-acetic acid ethyl ester (112 mg, 0.25 mmol) in ethanol (5 ml) and 2M sodium hydroxide (1 ml, 2mmol) was stirred at  
25 room temperature for 1 hour then diluted with water and 1:1 diethyl ether/iso-hexane. The aqueous suspension was separated, acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic solution was dried ( $\text{MgSO}_4$ ) evaporated to dryness and the residue triturated with iso-hexane to give the title compound as a white solid (86 mg, 80%).  
 $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.56 (2H, s), 4.78 (2H, br s), 6.71 (1H, d,  $J=8\text{Hz}$ ), 7.10-7.59 (15H, m).  
LC/MS  $t=3.86$ ,  $[\text{MH}^-]$  427, 429

30

Examples 3 and 4 were prepared in a similar manner:

Example 3: (2-Benzyloxy-5-chloro[1,1';2',1'']terphenyl-2''-yl)acetic acid

35 a) 1-(2'-Bromo-biphenyl-2-yl)-ethanone

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.36 (3H, s), 7.38-7.91 (8H, m).

LC/MS t=3.31, [MH+]<sup>+</sup>276.9

b) (2'-Bromo-biphenyl-2-yl)-acetic acid methyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 3.47 (2H, q), 3.56 (3H, s), 7.16-7.64 (7H, m), 7.65 (1H, d).

5

c) (2-Benzyloxy-5-chloro[1,1':2',1'']terphenyl-2''-yl)acetic acid ethyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.15 (3H, t, J=7Hz), 3.20 (1H, br d), 3.43 (1H, d, J=16Hz), 4.03 (2H, q, J=7Hz), 4.86 (2H, q), 6.61 (1H, d), 6.99-7.40 (15H, m).

10 d) (2-Benzyloxy-5-chloro[1,1':2',1'']terphenyl-2''-yl)acetic acid

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 3.18 (1H, br d), 3.44 (1H, d, J=16Hz), 4.83 (2H, q), 6.60 (1H, d, J=9Hz), 7.02-7.40 (15H, m).

LC/MS t=3.81, [MH-]<sup>-</sup> 427, 429.1

15 **Example 4: (2-Benzyloxy-5-chloro[1,1':2',1'']terphenyl-4''-yl)acetic acid**

a) 1-(2'-Bromo-biphenyl-4-yl)-ethanone

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.66 (3H, s), 7.25-7.39 (3H, m), 7.52 (2H, d, J=8Hz), 7.69 (1H, d, J=8Hz), 8.03 (2H, d, J=8Hz).

20 LC/MS t=3.45, [MH+]<sup>+</sup> 274.9

b) (2'-Bromo-biphenyl-4-yl)-acetic acid methyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 3.68 (2H, s), 3.73 (3H, s), 7.17-7.40 (7H, m), 7.67 (1H, d, J=8Hz)

25 c) (2-Benzyloxy-5-chloro[1,1':2',1'']terphenyl-4''-yl)acetic acid ethyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.22 (3H, t, J=7Hz), 3.56 (2H, s), 4.14 (2H, q, J=7Hz), 4.64 (2H, br s), 6.61 (1H, d, J=8Hz), 6.99-7.41 (15H, m).

d) (2-Benzyloxy-5-chloro[1,1':2',1'']terphenyl-4''-yl)acetic acid

30 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 3.61 (2H, s), 4.62 (2H, br s), 6.59 (1H, d, J=8Hz), 6.98-7.42 (15H, m).

**Example 5: 5''-Acetylamino-2-benzyloxy-5-chloro[1,1':2',1'']terphenyl-3''-carboxylic acid**

35 a) 5-Amino-2'-bromobiphenyl-3-carboxylic acid methyl ester

A mixture of (3-amino-5-methoxycarbonylphenyl)boronic acid (1.02 g, 5.23 mmol), 1,2-dibromobenzene (2.47g, 10.46 mmol), potassium carbonate (5.52 g, 40 mmol) and tetrakis(triphenylphosphine)palladium(0) (606 mg, 0.523 mmol) in 1:1 toluene/ethanol (30 ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was purified using Biotage with ethyl acetate/iso-hexane (3:17) to yield the title compound as a colourless gum (1.21g, 76%).

40

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.86 (2H, br s), 3.90 (3H, s), 6.90 (1H, s), 7.19-7.38 (4H, m), 7.45 (1H, s), 7.65 (1H, d,  $J=8\text{Hz}$ ).

b) 5"-Amino-2-benzyloxy-5-chloro[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester

5 A mixture of 2-benzyloxy-5-chloro-phenyl-boronic acid (197 mg, 0.75 mmol), 5-amino-2'-bromo-biphenyl-3-carboxylic acid methyl ester (216 mg, 0.71 mmol), potassium carbonate (828 mg, 6 mmol) and tetrakis(triphenylphosphine)palladium(0) (79 mg, 0.068mmol) in 1:1 toluene/ethanol (8 ml) was stirred and heated at  $90^\circ\text{C}$  under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was purified using Biotage with ethyl acetate/iso-hexane (1:4) to yield the title compound as a pale yellow gum. (288 mg, 89%).

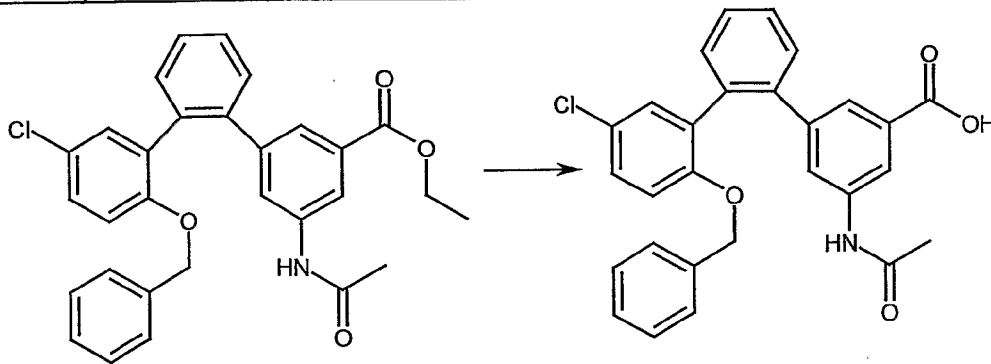
10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.25 (3H, t,  $J=7\text{Hz}$ ), 3.52 (2H, br s), 4.23 (2H, q,  $J=7\text{Hz}$ ), 4.68 (2H, br s), 6.52 (1H, s), 6.63 (1H, d,  $J=9\text{Hz}$ ), 7.00-7.41 (13H, m).  
LC/MS  $t=3.93$ ,  $[\text{MH}^+]$  458.2, 460.2.

c) 5"-Acetylamino-2-benzyloxy-5-chloro[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester

Acetic anhydride (53 mg, 0.5 mmol) was added to a solution of 5"-amino-2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester (96 mg, 0.21mmol) in pyridine (2 ml) and the mixture left at room temperature for 1 hour. The resulting solution was diluted with diethyl ether, washed with 1M hydrochloric acid and saturated sodium bicarbonate solution, dried (MgSO<sub>4</sub>) and evaporated to dryness to yield the title compound as a colourless gum. (102 mg, 97%).

20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.29 (3H, t,  $J=7\text{Hz}$ ), 2.10 (3H, s), 4.25 (2H, q), 4.70 (2H, br d), 6.63 (1H, d,  $J=9\text{Hz}$ ), 6.99-7.43 (12H, m), 7.50 (1H, s), 8.00 (1H, s).  
LC/MS  $t=3.86$ ,  $[\text{MH}^+]$  500, 502.1.

d) 5"-Acetylamino-2-benzyloxy-5-chloro[1,1';2',1'']terphenyl-3"-carboxylic acid



30 5"-Acetylamino-2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester (102 mg, 0.2 mmol) was dissolved in a mixture of ethanol (5 ml) and 2M sodium hydroxide (1 ml, 2 mmol) and left at room temperature for 5 hours. The resulting solution was diluted with water, washed with diethyl ether and the aqueous phase separated, acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic phase was dried (MgSO<sub>4</sub>) and evaporated to dryness to yield the title compound as a white solid. (81 mg, 84%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.12 (3H, s), 4.70 (2H, br d), 6.65 (1H, d,  $J=8\text{Hz}$ ), 7.00-7.45 (12H, m), 7.58 (1H, s), 8.07 (1H, s).  
LC/MS  $t=3.59$ ,  $[\text{MH}]^-$  470.1, 472.1.

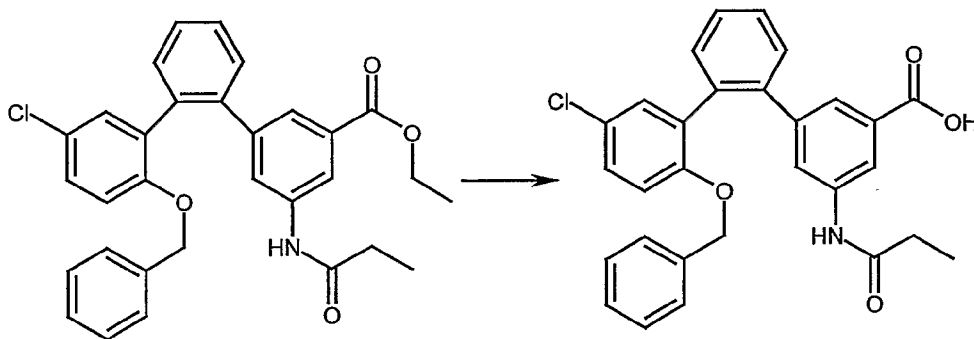
5 **Example 6: 2-Benzyloxy-5-chloro-5"-propionylamino[1,1';2'1'']terphenyl-3"-carboxylic acid**

a) 2-Benzyloxy-5-chloro-5"-propionylamino[1,1';2'1'']terphenyl-3"-carboxylic acid ethyl ester

10 Propionyl chloride (10 mg, 0.11 mmol) was added to a solution of 5"-amino-2-benzyloxy-5-chloro-[1,1',2',1'']terphenyl-3"-carboxylic acid ethyl ester (47 mg, 0.1 mmol) and triethylamine (12 mg, 0.12 mmol) in dichloromethane (2 ml) and the mixture left at room temperature for 2 hours. The resulting solution was diluted with diethyl ether, washed with 1M hydrochloric acid and saturated sodium bicarbonate solution then dried ( $\text{MgSO}_4$ ) and  
15 evaporated to dryness. The residue was purified by chromatography using Biotage with ethyl acetate/iso-hexane (1:3) to yield the title compound as a colorless gum. (49 mg, 95%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.21 (3H, t,  $J=7\text{Hz}$ ), 1.30 (3H, t,  $J=7\text{Hz}$ ), 2.30 (2H, q,  $J=7\text{Hz}$ ), 4.25 (2H, q,  $J=7\text{Hz}$ ), 4.68 (2H, br d), 6.63 (1H, d,  $J=9\text{Hz}$ ), 6.88 (1H, s), 7.00-7.50 (13H, m), 8.03 (1H, s). LC/MS  $t=4.03$ ,  $[\text{MH}]^+$  514.2, 516.2.

b) 2-Benzyloxy-5-chloro-5"-propionylamino[1,1';2'1'']terphenyl-3"-carboxylic acid



25 2-Benzyloxy-5-chloro-5"-propionylamino-[1,1',2',1'']terphenyl-3"-carboxylic acid ethyl ester (49 mg, 0.095 mmol) was dissolved in ethanol (5 ml) and 1M sodium hydroxide (1 ml, 1 mmol) and left at room temperature for 5 hours. The resulting solution was diluted with water acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic phase was dried ( $\text{MgSO}_4$ ) evaporated to dryness and triturated with iso-hexane to yield the title compound as an off-white solid. (31 mg, 67%).

30  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.21 (3H, t,  $J=7\text{Hz}$ ), 2.33 (2H, q,  $J=7\text{Hz}$ ), 4.70 (2H, br d), 6.65 (1H, d,  $J=9\text{Hz}$ ), 6.90 (1H, s), 7.03-7.46 (12H, m), 7.57 (1H, s), 8.10 (1H, s).  
LC/MS  $t=3.75$ ,  $[\text{MH}]^-$  484.3, 486.2.

Examples 7 to 9 were prepared in a similar manner:

**Example 7: 2-Benzoyloxy-5-chloro-5''-(2-methylpropanoylamino)-[1,1';2',1'']terphenyl-3''-carboxylic acid**

- 5 a) 2-Benzoyloxy-5-chloro-5''-(2-methylpropanoylamino)-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.20 (3H, s), 1.22 (3H, s), 1.30 (3H, t, J=7Hz), 2.42 (1H, m), 4.25 (2H, q, J=7Hz), 4.70 (2H, br d), 6.63 (1H, d, J=9Hz), 6.90-7.50 (14H, m), 8.02 (1H, s).  
LC/MS t=4.11, [MH<sup>+</sup>] 528.3, 530.2.

10

- b) 2-Benzoyloxy-5-chloro-5''-(2-methylpropanoylamino)-[1,1';2',1'']terphenyl-3''-carboxylic acid

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.17 (3H, s), 1.21 (3H, s), 2.43 (1H, m), 4.70 (2H, br d), 6.66 (1H, d, J=9Hz), 6.91 (1H, s), 7.03-7.47 (12H, m), 7.57 (1H, s), 8.10 (1H, s).

15 LC/MS t=3.85, [MH<sup>-</sup>] 498.2, 500.2.

**Example 8: 2-Benzoyloxy-5''-butyrylamino-5-chloro[1,1';2',1'']terphenyl-3''-carboxylic acid**

- 20 a) : 2-Benzoyloxy-5''-butyrylamino-5-chloro[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.95 (3H, t, J=7Hz), 1.29 (3H, t, J=7Hz), 1.70 (2H, m), 2.26 (2H, t, J=7Hz), 4.25 (2H, q, J=7Hz), 4.70 (2H, br d), 6.63 (1H, d, J=9Hz), 6.91 (1H, s), 7.01-7.51 (12H, m), 8.02 (1H, s).

25 LC/MS t=4.12, [MH<sup>+</sup>] 528.1, 530.1.

- b) : 2-Benzoyloxy-5''-butyrylamino-5-chloro[1,1';2',1'']terphenyl-3''-carboxylic acid

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.99 (3H, t, J=7Hz), 1.72 (2H, m), 2.27 (2H, t, J=7Hz), 4.71 (2H, br d), 6.65 (1H, d, J=9Hz), 6.87 (1H, s), 7.02-7.46 (12H, m), 7.58 (1H, s), 8.09 (1H, s).

30 LC/MS t=3.86, [MH<sup>-</sup>] 498.1, 500.1.

**Example 9: 2-Benzoyloxy-5-chloro-5''-[(1-phenyl-methanoyl)amino]-[1,1';2',1'']terphenyl-3''-carboxylic acid**

- 35 a) 2-Benzoyloxy-5-chloro-5''-[(1-phenyl-methanoyl)amino]-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.26 (3H, t, J=7Hz), 4.26 (2H, q, J=7Hz), 4.70 (2H, br d), 6.65 (1H, J=9Hz), 7.02-7.57 (16H, m), 7.79 (2H, m), 8.15 (1H, s).

LC/MS t=4.22, [MH<sup>+</sup>] 562.2, 564.2.

40

- b) 2-Benzoyloxy-5-chloro-5''-[(1-phenyl-methanoyl)amino]-[1,1';2',1'']terphenyl-3''-carboxylic acid

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 4.70 (2H, br d), 6.67 (1H, d,  $J=9\text{Hz}$ ), 7.04-7.61 (17H, m), 7.80 (2H, d,  $J=7\text{Hz}$ ), 8.23 (1H, s).

LC/MS  $t=4.01$ ,  $[\text{MH}]^-$  532.2, 534.3.

5 **Example 10: 2-Benzyloxy-5-chloro-5"-methanesulfonylamino-[1,1';2',1'']terphenyl-3"-carboxylic acid**

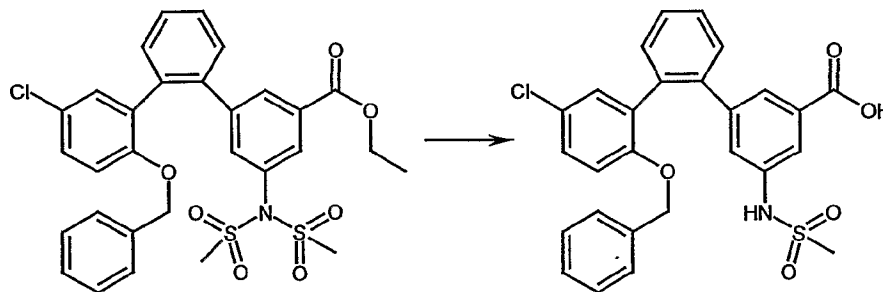
a) 2-Benzyloxy-5-chloro-5"-dimethanesulfonylamino-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester

10 Methanesulphonyl chloride (25 mg, 0.22 mmol) was added to a solution of 5"-amino-2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester (47 mg, 0.1 mmol) and triethylamine (25 mg, 0.25 mmol) and the mixture left at room temperature for 3 hours. The resulting solution was diluted with diethyl ether, washed with 1M hydrochloric acid and saturated sodium bicarbonate solution then dried ( $\text{MgSO}_4$ ) and evaporated to dryness.

15 The residue was purified by chromatography using Biotage with ethyl acetate/iso-hexane (1:4) to yield the title compound as a colorless gum. (56 mg, 91%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.26 (3H, t,  $J=7\text{Hz}$ ), 3.14 (6H, br d), 4.18 (2H, br s), 4.48 (1H, br d), 4.69 (1H, br d), 6.66 (1H, d,  $J=9\text{Hz}$ ), 6.94-7.51 (12H, m), 7.80 (1H, s), 7.95 (1H, s).

20 b) 2-Benzyloxy-5-chloro-5"-methanesulfonylamino-[1,1';2',1'']terphenyl-3"-carboxylic acid



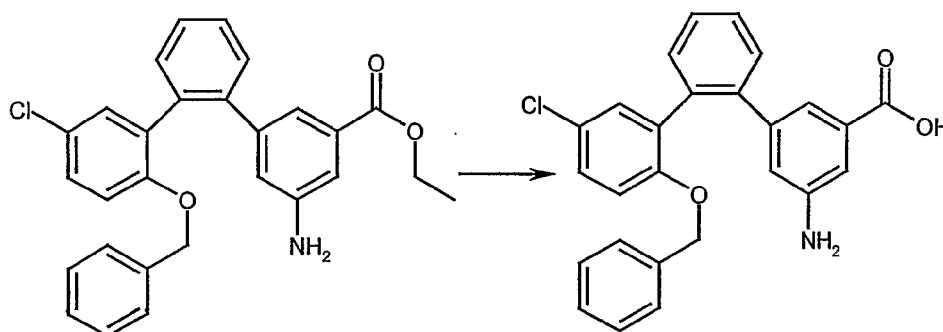
2-Benzyloxy-5-chloro-5"-dimethanesulfonylamino-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester was dissolved in ethanol (5 ml) and 1M sodium hydroxide (1 ml, 1 mmol) and left at room temperature for 5 hours then heated at  $50^\circ\text{C}$  for 1 hour. The resulting solution was diluted with water, acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic phase was dried ( $\text{MgSO}_4$ ), evaporated to dryness and triturated with diethyl ether/iso-hexane to yield the title compound as a white solid. (21 mg, 46%).

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 2.67 (3H, s), 4.85 (2H, br s), 6.91 (1H, d,  $J=9\text{Hz}$ ), 7.03-7.53 (13H, m), 7.67 (1H, s), 9.87 (1H, s), 12.9 (1H, br s).

LC/MS  $t=3.68$ ,  $[\text{MH}]^-$  506.2, 508.2.

**Example 11: 5"-Amino-2-benzyloxy-5-chloro[1,1';2',2'']-terphenyl-3"-carboxylic acid**





5'-Amino-2-benzyloxy-5-chloro-[1,1',2',1'']terphenyl-3''-carboxylic acid ethyl ester (192 mg, 0.42 mmol) was dissolved in ethanol (5 ml) and 2M sodium hydroxide (2 ml, 4 mmol) and heated at 60°C for 1 hour. The resulting solution was diluted with water acidified with acetic acid and extracted with diethyl ether. The organic phase was dried (MgSO<sub>4</sub>) evaporated to dryness and triturated with iso-hexane/diethyl ether to yield the title compound as a white solid. (141 mg, 78%).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ: 4.9 (2H, br s), 5.23 (2H, br s), 6.58 (1H, s), 6.89 (1H, s), 6.95 (1H, d, J=9Hz), 7.02 (1H, dd, J=9Hz, 2Hz), 7.13 (1H, d, J=9Hz), 7.24-7.41 (10H, m), 12.4 (1H, br s).

LC/MS t=3.59 [MH<sup>-</sup>] 470.1, 472.1.

#### **Example 12: 2-Benzyloxy-5''-butyrylamino-5-trifluoromethyl[1,1';2',1'']terphenyl-3''-carboxylic acid**

##### **a) 2'-Bromo-5-butyrylamino-biphenyl-3-carboxylic acid methyl ester**

Butyryl chloride (55 mg, 0.52 mmol) was added to a solution of 5-amino-2'-bromo-biphenyl-3-carboxylic acid methyl ester (153 mg, 0.5 mmol) and triethylamine (76 mg, 0.75 mmol) in dichloromethane (5 ml) and the mixture left at room temperature for 30 minutes.

The resulting solution was diluted with diethyl ether, washed with 1M hydrochloric acid and saturated sodium bicarbonate, dried (MgSO<sub>4</sub>) and evaporated to dryness to yield the title compound as a light yellow gum. (161 mg, 88%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.01 (3H, t, J=7Hz), 1.77 (2H, m), 2.37 (2H, t, J=7Hz), 3.92, (3H,s), 7.20-7.36 (3H, m), 7.43 (1H, br s), 7.66 (1H, d, J=8Hz), 7.83 (1H, s), 7.94 (1H, s), 8.10 (1H, s). LC/MS t=3.54, [MH<sup>+</sup>] 378.

##### **b) 4-Benzyloxy-3-bromobenzotrifluoride**

A solution of 3-bromo-4-hydroxybenzotrifluoride (6.03g, 25mmol) in acetone (100ml) was treated with benzyl bromide (4.67g, 3.25ml, 27.5mmol) and potassium carbonate (5.18g, 37.5mmol). The mixture was stirred and heated to reflux under nitrogen for 2h. After cooling, diethyl ether (300ml) and water (300ml) were added and the aqueous phase re-extracted with diethyl ether (100ml). The combined organic layers were washed with water, dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. The orange oil was flash

chromatographed (silica gel, 2-5% dichloromethane-isohehexane) to give the title compound as a clear oil (7.0g, 85%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 5.22 (2H, s), 6.98 (1H, d, J = 9Hz), 7.34-7.51 (6H, m), 7.83 (1H, s).

The product contains a trace impurity that can be removed by recrystallisation from isohehexane at -78°C.

c) 2-Benzyloxy-5-trifluoromethylbenzeneboronic acid

A solution of 4-benzyloxy-3-bromobenzotrifluoride (4.48g, 13.54mmol) in tetrahydrofuran (100ml) was cooled to -100°C (diethyl ether/liquid nitrogen) with stirring under nitrogen.

1.6M n-butyllithium in hexanes (9.3ml, 14.89mmol) was added over 20mins. at -100°C and the mixture warmed to -78°C (acetone/Drikold) and stirred for 1h. Triisopropylborate (7.64g, 9.38ml, 40.66mmol) was added dropwise at -78°C and the reaction stirred and allowed to warm to room temperature over 1.5h. 1M Hydrochloric acid (100ml) was added and the mixture stirred vigorously for 1h. The layers were separated and the aqueous layer extracted with diethyl ether (50ml). The combined organic phases were washed with water, dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. The yellow waxy solid was flash chromatographed (silica gel, 4-20% EtOAc-isohehexane) and the product triturated with hexane. The white solid was filtered and dried *in vacuo* to give the title compound (1.53g, 38%).

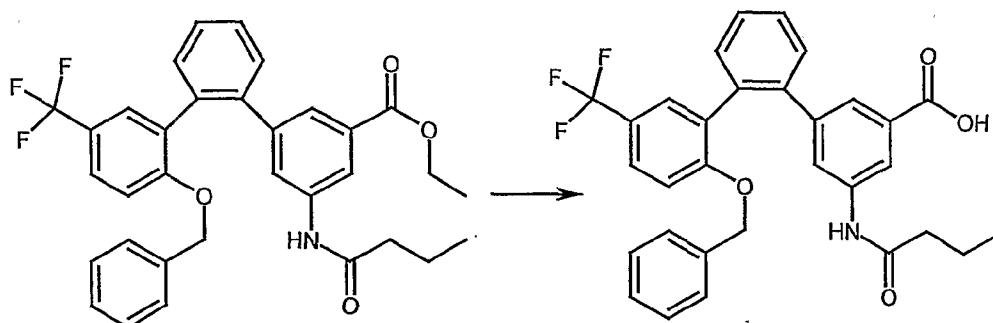
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 5.20 (2H, s), 5.76 (2H, s), 7.05 (1H, d, J = 9Hz), 7.42-7.44 (5H, m); 7.68 (1H, dd J = 2Hz, J = 9Hz), 8.15 (1H, s).

d) 2-Benzyloxy-5"-butyrylamino-5-trifluoromethyl[1,1':2',1'']terphenyl-3"-carboxylic acid ethyl ester

A mixture of 2-benzyloxy-5-trifluoromethyl-phenyl-boronic acid (38 mg, 0.13 mmol), 2'-bromo-5-butyrylamino-biphenyl-3-carboxylic acid methyl ester (45 mg, 0.12 mmol), potassium carbonate (138 mg, 1 mmol) and tetrakis(triphenylphosphine)palladium(0) (14 mg, 0.012 mmol) in 1:1 toluene/ethanol (3 ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was purified using Biotage with ethyl acetate/iso-hexane (1:4) to yield the title compound as a colourless gum (51 mg, 76%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.97 (3H, t, J=7Hz), 1.26 (3H, t, J=7Hz), 1.71 (2H, m), 2.25 (2H, t, J=7Hz), 4.23 (2H, q, J=7Hz), 6.75 (1H, d, J=8Hz), 6.89 (1H, s), 7.02 (2H, m) 7.24-7.47 (11H, m), 7.51 (1H, s), 7.97 (1H, s). LC/MS t=4.13, [MH-] 560.2.

e) 2-Benzyloxy-5"-butyrylamino-5-trifluoromethyl[1,1':2',1'']terphenyl-3"-carboxylic acid



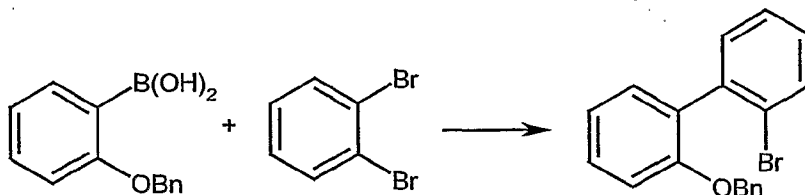
2-Benzyloxy-5'-butyrylamino-5-trifluoromethyl-[1,1',2',1'']terphenyl-3"-carboxylic acid ethyl ester (51 mg, 0.091 mmol) was dissolved in ethanol (5 ml) and 2M sodium hydroxide (1 ml, 2 mmol) and left at room temperature for 18 hours. The resulting solution was diluted with water acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic phase was dried (MgSO<sub>4</sub>) evaporated to dryness and triturated with iso-hexane to yield the title compound as an off-white solid. (40 mg, 83%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.97 (3H, t, J=7Hz), 1.71 (2H, m), 2.26 (2H, t, J=7Hz), 4.82 (2H, br s), 6.78 (1H, d, J=9Hz), 6.88 (1H, s), 7.04 (2H, d, J=7Hz), 7.25-7.48 (10H, m), 7.54 (1H, s), 8.03 (1H, s).

LC/MS t=3.87, [MH-] 532.2.

### **Example 13: 2-Benzyloxy-4"-chloro[1,1';2',1'']terphenyl 2"-carboxylic acid**

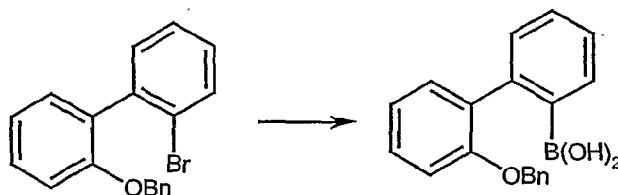
a) 2'-Benzyloxy-2-bromobiphenyl



A solution of 2-benzyloxyphenylboronic acid (4.3g, 19.3mmol) and 1,2-dibromobenzene (9.11g, 4.66ml, 38.6mmol) in 1:1 toluene: ethanol (150ml) was stirred under nitrogen and tetrakis(triphenylphosphine)palladium(0) (1.12g, 0.95mmol) and potassium carbonate (21.3g, 154mmol) added. The reaction was stirred at 90°C under nitrogen for 2 hours. After cooling, diethyl ether (100ml) and water (100ml) were added and the organic phase separated. The aqueous phase was extracted with diethyl ether (50ml) and the combined organic layers washed with water, dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. The residue was flash chromatographed (silica gel, 5-15% CH<sub>2</sub>Cl<sub>2</sub>-isohexane) to give the title compound as a clear oil (4.53g, 69%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 5.07 (2H, s), 7.02 (2H, m), 7.19-7.34 (10H, m), 7.65 (1H, d, J = 8Hz).

b) 2'-Benzyloxy-biphenyl-2-boronic acid

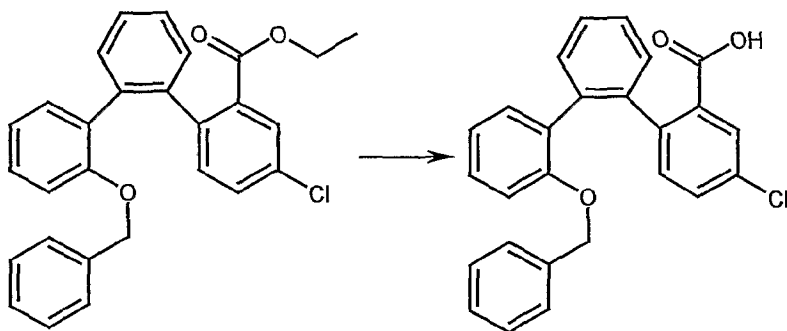


A solution of 2'-benzyloxy-2-bromobiphenyl (2.41g, 7.09mmol) in tetrahydrofuran (50ml) was stirred under nitrogen and cooled to  $-100^{\circ}\text{C}$  (diethyl ether/liquid nitrogen). 1.6M  $n\text{BuLi}$  in hexanes (4.87ml, 7.80mmol) was added over 15 mins. at  $-100^{\circ}\text{C}$  and the mixture warmed to  $-78^{\circ}\text{C}$  (acetone/Drikold) and stirred for 1h. Triisopropyl borate (4.00g (5.02ml, 21.30mmol) was added at  $-78^{\circ}\text{C}$  and the reaction allowed to warm to room temperature with stirring over 1.5h. 1M Hydrochloric acid (50ml) was added and the mixture stirred vigorously for 1h. The organic layer was separated and the aqueous layer extracted with diethyl ether (50ml). The combined organic phase were washed with water, dried ( $\text{MgSO}_4$ ) and the solvent removed *in vacuo*. The yellow oil was flash chromatographed (silica gel, 10-20% EtOAc-isohexane) to give the title compound as a clear oil (1.74g, 80%). LC/MS RT = 3.28min [(2M- $\text{H}_2\text{O}$ )H-] = 589.3

c) 2-Benzyloxy-4"-chloro-[1,1':2',1'']terphenyl-2"-carboxylic acid ethyl ester

A mixture of 2'-benzyloxy-biphenyl-2-boronic acid (61 mg, 0.2 mmol), ethyl 2-bromo-5-chlorobenzoate (53 mg, 0.2 mmol), potassium carbonate (207 mg, 1.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.02 mmol) in 1:1 toluene/ethanol (3 ml) was stirred and heated at  $90^{\circ}\text{C}$  under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried ( $\text{MgSO}_4$ ) and evaporated to dryness. The residue was purified using Biotage with ethyl acetate/iso-hexane (1:19) to yield the title compound as a colourless gum (63 mg, 71%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.97 (3H, br s), 3.99 (2H, br s), 4.87 (2H, br q), 6.75-6.81 (2H, m), 6.98-7.02 (2H, m), 7.14-7.41 (11H, m), 7.65 (1H, d,  $J=2\text{Hz}$ ).

d) 2-Benzyloxy-4"-chloro[1,1':2',1'']terphenyl-2"-carboxylic acid



2-Benzyloxy-4"-chloro-[1,1':2',1'']terphenyl-2"-carboxylic acid ethyl ester (58 mg, 0.137 mmol) was dissolved in ethanol (5 ml) and 2M sodium hydroxide (1 ml, 2 mmol) and heated at  $75^{\circ}\text{C}$  for 9 hours. The resulting solution was diluted with water, washed with isohexane and the aqueous suspension separated, acidified with 1M hydrochloric acid and extracted with diethyl ether. The organic phase was dried ( $\text{MgSO}_4$ ) evaporated to dryness

and triturated with iso-hexane/diethyl ether to yield the title compound as a white solid. (26 mg, 48%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 4.91 (2H, br d), 6.71 (1H, d, J=8Hz), 6.80-7.47 (14H, m), 7.69 (1H, d, J=2Hz). LC/MS t=3.95, [MH<sup>-</sup>] 413, 415.

5

Examples 14 to 18 were prepared in a similar manner:

**Example 14: 2-Benzylxy-5"-fluoro-[1,1';2',1'']terphenyl-2"-carboxylic acid**

10 a) 2-Benzylxy-5"-fluoro-[1,1';2',1'']terphenyl-2"-carboxylic acid ethyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.94 (3H, br s), 3.98 (2H, br s), 4.90 (2H, br q), 6.76-6.79 (3H, m), 6.85-7.42 (12H, m), 7.70 (1H, dd, J=9Hz).

b) 2-Benzylxy-5"-fluoro-[1,1';2',1'']terphenyl-2"-carboxylic acid

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 4.89 (2H, br q), 6.73 (2H, m), 6.80-7.45 (13H, m), 7.74 (1H, dd, J=9Hz). LC/MS t=3.76, [MH<sup>-</sup>] 397.

**Example 15: 2-Benzylxy-4"-fluoro-[1,1';2',1'']terphenyl-2"-carboxylic acid**

20 a) 2-Benzylxy-4"-fluoro-[1,1';2',1'']terphenyl-2"-carboxylic acid ethyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.96 (3H, br s), 3.99 (2H, br s), 4.88 (2H, br q), 6.76-6.78 (2H, m), 7.02-7.41 (14H, m).

b) 2-Benzylxy-4"-fluoro-[1,1';2',1'']terphenyl-2"-carboxylic acid

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 4.91 (2H, br d), 6.71 (1H, d, J=8Hz), 6.80-7.47 (15H, m). LC/MS t=3.79, [MH<sup>-</sup>] 397.

**Example 16: 2"-Benzylxy-5-fluoro-[1,1';2',1'']terphenyl-3-carboxylic acid**

30 a) 2"-Benzylxy-5-fluoro-[1,1';2',1'']terphenyl-3-carboxylic acid ethyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.30 (3H, t, J=7Hz), 4.27 (2H, q, J=7Hz), 4.72 (2H, br d), 6.76 (1H, d, J=8Hz), 6.90-6.93 (2H, m), 7.04 (2H, d), 7.16-7.50 (10H, m), 7.63 (1H, s).

b) 2"-Benzylxy-5-fluoro-[1,1';2',1'']terphenyl-3-carboxylic acid

35 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 4.78 (2H br d), 6.77 (1H, d, J=8Hz), 6.92-7.06 (4H, m), 7.16-7.45 (9H, m), 7.56, (1H, d, J=8Hz), 7.69 (1H, s). LC/MS t=3.98, [MH<sup>-</sup>] 397.1.

**Example 17: 4"-Amino-2-benzylxy-[1,1';2',1'']terphenyl-3"-carboxylic acid**

40 a) 4"-Amino-2-benzylxy-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.21 (3H, t, J=7Hz), 4.18, (2H, q, J=7Hz), 5.62 (2H, br s), 6.39 (1H, d, J=8Hz), 6.75, (1H, d, J=8Hz), 6.86-6.96 (2H, m), 7.04 (1H, d, J=7Hz), 7.16-7.41 (10H, m), 7.71 (1H, d, J=2Hz). LC/MS t=4.04, [MH<sup>+</sup>] 424.1.

b) 4''-Amino-2-benzyloxy-[1,1';2',1'']terphenyl-3''-carboxylic acid

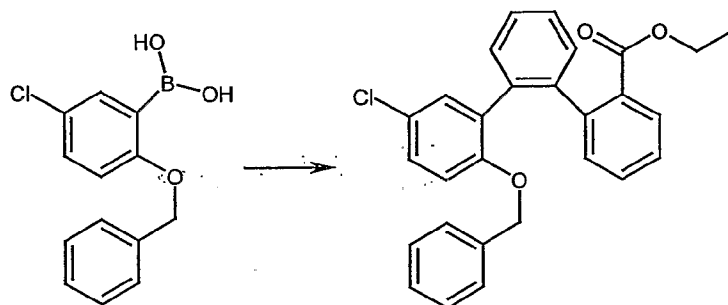
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 4.82 (2H, br s), 5.65 (2H, br s), 6.39 (1H, d, J=8Hz), 6.76 (1H, d, J=8Hz), 6.91 (1H, t), 6.96 (1H, dd), 7.06 (2H, d, J=7Hz), 7.15-7.41 (9H, m), 7.77 (1H, d, J=2Hz). LC/MS t=3.72, [MH-] 394.2.

**Example 18: 5''-Acetyl-amino-2-benzyloxy-[1,1';2',1'']terphenyl-2''-carboxylic acid**

LC/MS t=3.38 [MH-] 436.

**Example 19: 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2''-carboxylic acid**

a) 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester



A mixture of 2'-benzyloxy-5'-chlorophenylboronic acid (947mg, 3.61mmol), 2'-Bromo-biphenyl-2-carboxylic acid ethyl ester (1.0g, 3.28 mmol), potassium carbonate(3.39g, 24.6mmol), and tetrakis(triphenylphosphine)palladium (0) (379mg, 0.32mmol) in 1:1 toluene/ethanol (40ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water. The organic phase was dried and evaporated. The residue was chromatographed eluting with dichloromethane/isohexane (1:4 to 1:1) to yield the title compound as a colourless gum (1.28g, 88%).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.98(3H, br s), 4.09(2H, br s), 4.77(2H, m), 6.61(1H, d, J=9Hz), 7.0-7.4(14H, m), 7.69 (1H, d, J=8Hz). LC/MS t=4.09.

b) 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2''-carboxylic acid

The title compound was prepared in a manner similar to 2-benzyloxy-4''-chloro-[1,1';2',1'']terphenyl-2''-carboxylic acid.

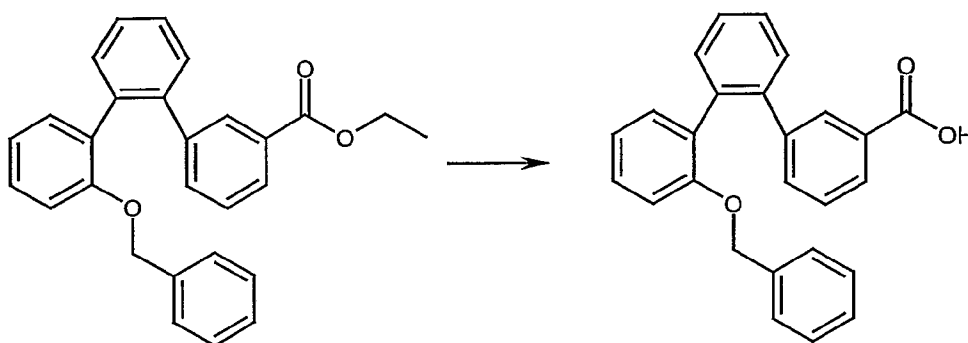
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 4.83(2H, m), 6.58(1H, d, J=9Hz), 6.95-7.33(14H, m), 7.75(1H, m)  
 LC/MS t=3.79, [MH-] 413.1, 415.1(1xCl).

**Example 20: 2-Benzyloxy-[1,1';2',1'']terphenyl-3''-carboxylic acid**

a) 2-Benzyloxy-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester

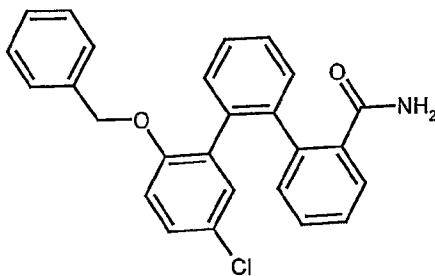
2'-Bromobiphenyl-3-carboxylic acid ethyl ester (153mg, 0.5mmol) and 2-benzyloxyphenylboronic acid (125mg (0.55mmol) were dissolved in 1:1 toluene:ethanol (5ml) under nitrogen. Potassium carbonate (552mg, 4mmol) and tetrakis(triphenylphosphine)palladium(0) (58mg, 0.05mmol) were added and the mixture heated at 90°C for 3 h. After cooling, the solvent was evaporated. The residue was partitioned between diethyl ether and water and the organic phase washed with water, dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. The residue was flash chromatographed (silica gel, 2-10% EtOAc-isohexane) to give the title compound as a clear oil (84mg, 41%). LC/MS Rt = 4.09 [(M-OEt)H<sup>+</sup>] = 363.1.

b) 2-Benzyloxy-[1,1';2',1'']terphenyl-3"-carboxylic acid



2-Benzyloxy-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester (84mg, 0.206mmol) was dissolved in ethanol (2ml) and 2M sodium hydroxide (0.5ml) added. The mixture was stirred and heated to 50°C for 4h. Water was added and the mixture extracted with isohexane. The aqueous layer was acidified with 2M hydrochloric acid and extracted with diethyl ether (2 x 10ml). The combined organic phases were washed with water, dried (MgSO<sub>4</sub>) and evaporated. The oil was triturated with isohexane and the resulting white solid filtered, washed with isohexane and dried *in vacuo*. (42mg, 54%).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 4.72 (2H, d (br)), 6.73 (1H, d, J = 8Hz) 6.92 (1H, t, J = 7Hz), 7.03 (2H, d, J = 7Hz), 7.15-7.26 (7H, m), 7.44 (4H, m), 7.89 (1H, d, J = 8Hz), 7.92 (1H, s).

Example 21: 2-Benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2"-carboxylic acid amide



A solution of 2-benzyloxy-5-chloro-[1,1';2',1'']terphenyl-2"-carboxylic acid (100mg 0.24mmol) in toluene(1ml) containing DMF (5 drops) was treated with thionyl chloride (0.035ml, 0.48mmol) and heated at 90°C for 1 hour. After cooling to room temperature the

solvent was evaporated. The residue was dissolved in tetrahydrofuran (1ml), aqueous ammonia (1ml) was added and the mixture stirred at room temperature for 3 hours. Addition of water (10ml) gave a precipitate which was filtered off and dried. (74mg 75%).

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 5.09(2H, s) 6.75-7.47(18H, m).

LC/MS  $t_r$ =3.57 [MH $^+$ ] 414.0, 416.0(1 Cl).

**Example 22: 5-(2-Benzyloxy-5-chloro-[1,1':2',1'']terphenyl-3"-yl)-1H-tetrazole**

**a) 2'-Bromo-biphenyl-3-carbonitrile**

A mixture of 3-cyanophenylboronic acid (735 mg, 5 mmol), 1,2-dibromobenzene (2.36 g, 10 mmol) potassium carbonate (6.9 g, 50 mmol) and tetrakis(triphenylphosphine)palladium(0) (580 mg, 0.5 mmol) in 1:1 toluene/ethanol (40 ml) was stirred and heated at 90°C under nitrogen for 3 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried (MgSO $_4$ ) and evaporated to dryness. The residue was purified by chromatography using Biotage with ethyl acetate/iso-hexane (1:19) to yield the title compound as a white solid (895 mg 69%).

$^1\text{H}$  NMR (CDCl $_3$ )  $\delta$ : 7.25-7.30 (3H, m), 7.40 (1H, t, J=7Hz), 7.54 (1H, t, J=7Hz), 7.65-7.71 (3H, m).

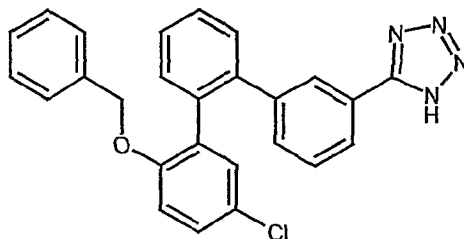
**b) 5-(2'-Bromo-biphenyl-3-yl)-1H-tetrazole**

A mixture of 2'-bromo-biphenyl-3-carbonitrile (200mg, 0.77mmol), sodium azide (66mg, 1.01mmol) and triethylamine hydrochloride (139mg, 1.01mmol) in toluene (2ml) was heated at 90°C for 24 hours. A further portion of sodium azide (66mg, 1.01mmol) and triethylamine hydrochloride (139mg, 1.01mmol) was added and heated for a further 24 hours. After cooling, the mixture was extracted with water (3x2ml). The combined extracts were acidified and the precipitate filtered off and dried. (163mg, 70%).

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 7.38-7.80(6H, m), 8.06-8.11(2H, m).

LC/MS  $t_r$ =3.82 [MH $^-$ ] 300.9 (1Br).

**c) 5-(2-Benzyloxy-5-chloro-[1,1':2',1'']terphenyl-3"-yl)-1H-tetrazole**



A mixture of 5-(2'-bromo-biphenyl-3-yl)-1H-tetrazole (163mg, 0.54mmol), 2-benzyloxy-5-chlorobenzeneboronic acid (156mg, 0.59mmol), potassium carbonate (589mg, 4.33mmol), and tetrakis(triphenylphosphine)palladium(0) (63mg, 0.05mmol) in 1:1 toluene/ethanol (5ml) was stirred and heated under nitrogen for 16 hours. After cooling the mixture was diluted with dichloromethane and water. The organic phase was dried and evaporated.

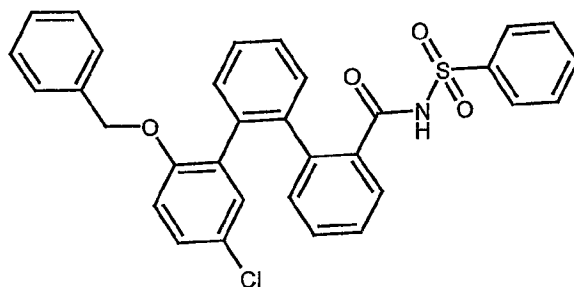


The residue was chromatographed eluting with dichloromethane/methanol (95:5) to give the title compound as a colourless solid. (120mg 51%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 4.75 (2H, br s), 6.63 (1H, d,  $J=8\text{Hz}$ ), 6.95-7.50 (14H, m), 7.88 (1H, m), 7.96 (1H, d,  $J=8\text{Hz}$ ). LC/MS  $t=4.22$  [MH $^+$ ] 439.0, 441.0 (1 Cl).

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**Example 23: N-[1-(2-Benzyloxy-5-chloro-[1,1';2,1'']terphenyl-2''-yl)-methanoyl]-benzenesulfonamide**



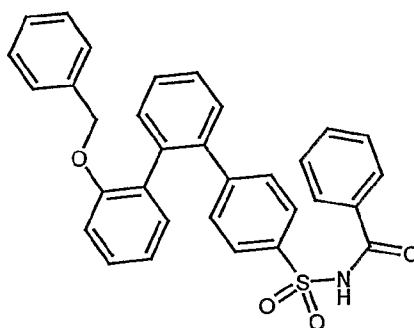
A mixture of 2-benzyloxy-5-chloro-[1,1';2,1'']terphenyl-2''-carboxylic acid (100mg, 0.24mmol), benzenesulphonamide (46mg, 0.29mmol), EDC (56mg, 0.29mmol), and 4-dimethylaminopyridine (5mg, 0.03mmol) in 1:1 dichloromethane/tetrahydrofuran(4ml) was stirred at room temperature for 16 hours. The mixture was diluted with ethyl acetate(10ml) and washed with aq. sodium bicarbonate (5ml), dilute hydrochloric acid (5ml), water(5ml), and brine (5ml). The organic phase was dried and evaporated. Purification by prep. HPLC gave the title compound.(27mg 20%).

15

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ :5.12(2H, q,  $J=10\text{Hz}$ ), 6.48(1H, d, $J=6\text{Hz}$ ), 6.6-7.8(19H, m), 9.23(1H, br s). LC/MS  $t=3.98$  [MH $^-$ ] 552.2,554.2 (1 Cl).

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**Example 24: 2-Benzyloxy-[1,1';2,1'']terphenyl-4''-sulfonic acid (1-phenyl-methanoyl)-amide**



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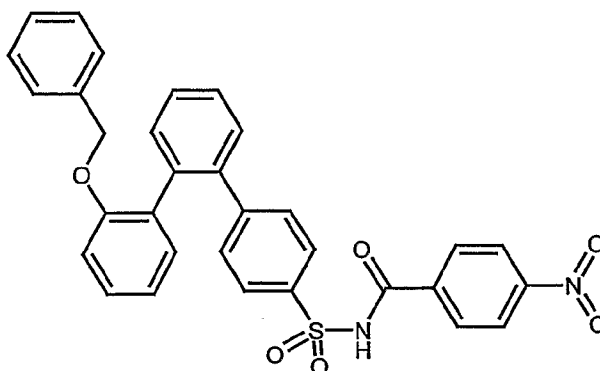
A mixture of 2'-benzyloxy-biphenyl-2-boronic acid (100mg, 0.33mmol), 4-bromo-N-(1-phenyl-methanoyl)-benzenesulfonamide (95mg, 0.28mmol), potassium carbonate (309mg, 2.24mmol), and tetrakis(triphenylphosphine)palladium(0) (38mg, 0.033mmol) in 1:1 toluene/ethanol (5ml) was stirred and heated at 90°C under nitrogen for 16 hours. After cooling the mixture was diluted with ethyl acetate and water. The organic phase was dried and evaporated. The residue was chromatographed eluting with ethyl acetate/iso-hexane (1:4-1:1) to give the title compound as a colourless solid.(40mg 23%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 4.6(2H, br d), 6.64(1H, d,  $J=8\text{Hz}$ ), 6.9-7.8(17H, m), 7.79(2H, d,  $J=8\text{Hz}$ ), 7.83(2H, d,  $J=8\text{Hz}$ ), 9.0(1H, br s). LC/MS  $t=4.09$   $[\text{MH}^+]$  520.1.

Examples 25 and 26 were prepared in a similar manner:

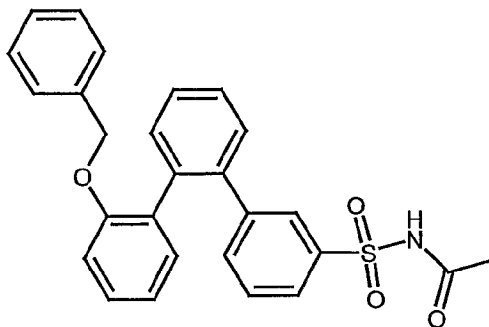
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**Example 25: 2-Benzyloxy-[1,1';2',1'']terphenyl-4"-sulfonic acid [1-(4-nitro-phenyl)-methanoyl]-amide**



10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 4.6(2H, br s), 6.59(1H, d,  $J=8\text{Hz}$ ), 6.8-7.9(20H, m). LC/MS  $t=4.57$   $[\text{MH}^-]$  563.

**Example 26: 2-Benzyloxy-[1,1';2',1'']terphenyl-3"-sulfonic acid acetyl-amide**



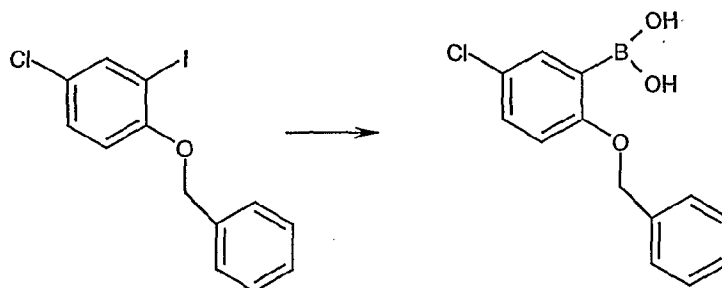
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$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.04(3H, s), 4.7(2H, br d), 6.70(1H, d,  $J=8\text{Hz}$ ), 6.92-7.46(14H, m), 7.74(1H, s), 7.84(1H, d,  $J=8\text{Hz}$ ), 8.1(1H, br s). LC/MS  $t=3.64$   $[\text{MH}^-]$  456.

**Preparation of Intermediates**

20

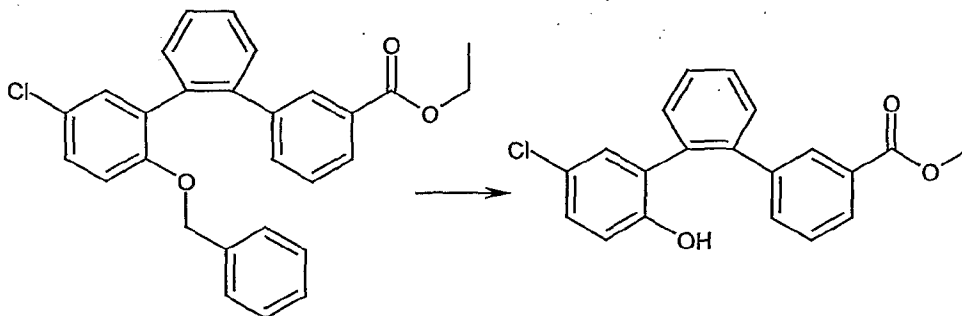
**2-Benzyloxy-5-chloro-phenyl-boronic acid**



Butyllithium (11.5 ml, 28.7 mmol, 2.5 M) was added, under nitrogen, over 10 minutes, to a solution of 2-benzyloxy-5-chloroiodobenzene (9 g, 26.2 mmol) in THF (40 ml) at -100°C. The reaction mixture was then warmed up at -78°C and stirred for 1 hour (at -78°C) before triisopropyl borate (18 ml, 78.4 mmol) was added over 10 minutes. The reaction mixture was then warmed to room temperature before a solution of HCl (60 ml, 1M) was added. The mixture was vigorously stirred for 1 1/2 hours. The organic phase was separated, washed sequentially with water and brine, dried (MgSO<sub>4</sub>) filtered and concentrated. The residue was triturated with a 30% solution of ether in iso-hexane and filtered to give the title compound (3.62g, 53%) as a white solid.

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 5.12(2H,s), 5.74(2H,s), 6.91(1H,d), 7.26(1H,s), 7.35-7.41(5H,m), 7.81(1H,s).

#### 5-Chloro-2-hydroxy-[1,1',2',1'']terphenyl-3"-carboxylic acid ethyl ester



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HBr (48% solution in acetic acid, 20 ml) was added to a solution of 2-benzyloxy-5-chloro-[1,1',2',1'']terphenyl-3"-carboxylic acid ethyl ester (690 mg, 1.5 mmol) in acetic acid (4 ml). The reaction mixture was stirred at room temperature for 30 minutes, then diluted with water and extracted with ether. The organic phase was washed with a saturated solution of NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>) and evaporated. The residue was redissolved in ethanol and a 30% aqueous ammonia solution (2 ml) was added. The reaction mixture was stirred overnight, concentrated in vacuo to an oil that was purified by chromatography, using Biotage®, with 15% of ethyl acetate in iso-hexane to yield the title compound (340 mg, 62%) as a yellow solid.

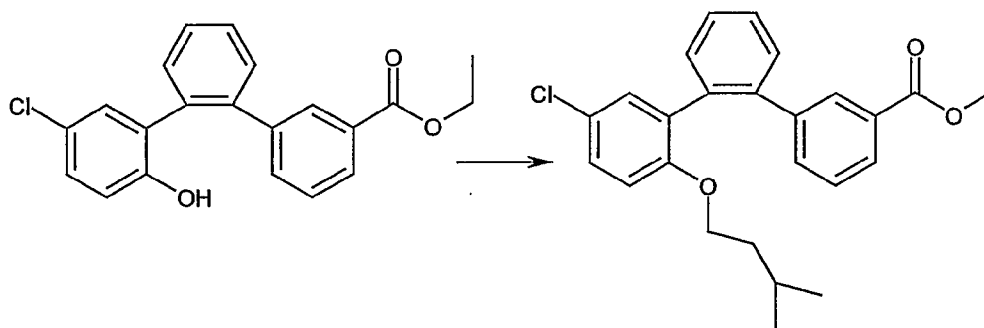
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.36 (3H, t), 4.33(2H, q), 6.68(1H, d), 7.08-7.93(10H, m).

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#### GENERAL PROCEDURE A - ALKYLATION

5-Chloro-2-(3-methyl-butoxy) -[1,1',2',1'']terphenyl-3"-carboxylic acid ethyl ester

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A mixture of 5-chloro-2-hydroxy-[1,1';2',1'']terphenyl-3'-carboxylic acid ethyl ester (50 mg, 0.14 mmol), potassium carbonate (48 mg, 0.35 mmol), and 1-bromo-3-methylbutane (23.5 mg, 0.15 mmol) was heated in N,N'-dimethylformamide (3 ml) at 90°C for 4 hours. The reaction mixture was then poured into water and extracted with ethyl acetate; the organic layers were dried over MgSO<sub>4</sub> and evaporated. The residue was chromatographed through a SPE column using 10% ethyl acetate in iso-hexane as eluent to yield the title compound as a white solid (45 mg, 75%).

<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.76(6H, d), 1.24-1.45 (6H,m), 3.24-3.70(2H,br.) 4.32 (2H,br.q), 6.58(1H,d), 7.13-7.43( 8H,m), 7.85(1H,d), 7.91(1H,s).

#### 5-Chloro-2-cyclopentylmethoxy -[1,1';2',1'']terphenyl-3'carboxylic acid ethyl ester

General procedure A was employed to synthesise 5-chloro-2-cyclopentylmethoxy -[1,1';2',1'']terphenyl-3'carboxylic acid ethyl ester using the toluene 4-sulfonic acid cyclopentyl methyl ester.

The toluene 4-sulfonic acid cyclopentyl methyl ester was prepared by adding p-Toluenesulfonyl chloride (3.6 mmol, 684 mg) to a solution of cyclopentanemethanol (3 mmol, 300mg) and pyridine(3ml)in dichloromethane(3ml). The resulting mixture was stirred for 2 1/2 hours at room temperature, then diluted with dichloromethane and washed sequentially with HCl (1M solution) and a saturated solution of Na<sub>2</sub>CO<sub>3</sub>. The organic layer was then dried over MgSO<sub>4</sub> and evaporated to give the toluene-4-sulfonic acid cyclopentyl methyl ester. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.17(2H,m), 1.53(4H,m), 1.69(2H,m), 2.20(1H,m), 2.45(3H,s), 3.89(2H,d), 7.34(2H,d), 7.78(2H,d).

The following intermediates were prepared following General Procedure A using the appropriate bromide as alkylating agent (all commercially available). <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> solution.

COMPOUND NAME	<sup>1</sup> H NMR
5-Chloro-2-(4-fluoro-benzyloxy) - [1,1';2',1'']terphenyl-3'carboxylic acid ethyl ester	1.32(3H,t), 4.12(2H,br.q), 4.52-4.82(2H,br.d), 6.59(1H,d), 6.91(2H, d), 7.11-7.87(12H, m).

5-Chloro-2-(2,4-difluoro-benzyloxy) - [1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester	1.33(3H,t), 4.12(2H,br.q), 4.52- 4.80(2H,br.d), 6.64 (1H,d), 6.70- 7.87(13H,m).
5-Chloro-2-(4-chloro-benzyloxy) - [1,1';2',1'']terphenyl-3"carboxylic acid ethyl ester	1.31(3H,t), 4.26(2H,br.q), 4.42- 4.78(2H,br.d), 6.56 (1H,d), 6.86(1H,d), 7.11-7.87(13H,m).
5-Chloro-2-(2-fluoro-4-chloro-benzyloxy) - [1,1';2',1'']terphenyl-3"carboxylic acid ethyl ester	1.32(3H,t), 4.12(2H,br.q), 4.45- 4.81(2H,br.s), 6.61 (1H,d),6.74(1H,t), 6.99 (2H,t), 7.14-7.87(10H, m).
5-Chloro-2-(4-isobutoxy)- [1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester	0.75(6H,d), 1.35(3H,t), 1.75- 1.80(1H,m), 3.34(2H, br. s), 4.32(2H, q), 6.62(1H, d), 7.09-7.43( 8H, m), 7.85(1H, d), 7.89(1H, s)
5-Chloro-2-(pyridin-2-ylmethoxy) - [1,1';2',1'']terphenyl-3"carboxylic acid ethyl ester	1.30(3H,t), 4.25(2H,q), 4.55- 4.89(2H,br.s), 6.58(1H,d), 6.73(1H,d), 7.11-7.87(12H, m), 8.47(1H, d).
5-Chloro-2-(pyridin-4-ylmethoxy) - [1,1';2',1'']terphenyl-3"carboxylic acid ethyl ester	1.30(3H,t), 4.25(2H,br. s), 4.55- 4.89(2H,br.d), 6.53(1H,d), 6.84(2H,d), 7.13-7.48(8H, m),7.80(1H,s), 7.86(1H,d) 8.46(2H, d).
5-Chloro-2-(pyridin-3-ylmethoxy) - [1,1';2',1'']terphenyl-3"carboxylic acid ethyl ester	1.32(3H,t), 4.28(2H, br.q), 4.40- 4.90(2H,br.d), 6.63 (1H,d) , 7.14- 7.85(12H, m),8.30(1H, s) 8.49(1H, d).
5-Chloro-2-cyclohexylmethoxy - [1,1';2',1'']terphenyl-3"carboxylic acid ethyl ester	0.75-1.72(14H, br. m), 3.28(2H,br.s), 4.32(2H,q), 6.62(1H,d), 7.11-7.44 (8H,m), 7.85(1H,d), 7.91(1H,s).
5-Chloro-2-(thiophen-3-ylmethoxy) - [1,1';2',1'']terphenyl-3"carboxylic acid ethyl ester	1.33(3H,t), 4.28(2H, br.q), 4.50- 4.82(2H,br.d), 6.64 (1H,d) , 6.75(1H, d), 6.84 (1H, d), 7.11-7.86(11H, m).
5-Chloro-2-(thiophen-2-ylmethoxy) - [1,1';2',1'']terphenyl-3"carboxylic acid ethyl ester	1.34(3H,t), 4.30(2H,q), 4.71- 4.84(2H,br.s), 6.71 (1H,d), 6.77- 7.85(13H, m).
5-Chloro-2-cyclopentylmethoxy - [1,1';2',1'']terphenyl-3"carboxylic acid ethyl ester	0.87-1.58(11H, m), 2.05 (1H,m), 3.46 (2H,br.s), 4.32(2H,q), 6.63 (1H,d), 7.08-7.43 (7H,m), 7.78 (1H,d), 7.85(1H,d), 7.90(1H, s).
5-Chloro-2-propoxy -[1,1';2',1'']terphenyl- 3"carboxylic acid ethyl ester	0.74(3H,t), 1.25(3H, t), 1.47 (2H,m), 3.30-3.75(2H, br.d), 4.31(2H,q), 6.58(1H, d), 7.11-7.43(8H,m), 7.85 (1H,s), 7.89(1H,s).

2-Butoxy-5-chloro-[1,1';2',1'']terphenyl-3-carboxylic acid ethyl ester	0.78(3H,t), 0.79-0.88 (1H,m), 1.15-1.21 (1H,m), 1.34(3H, t), 1.39-1.44 (2H,m), 3.29-3.75 (2H, br.d), 4.29(2H,q), 6.70 (1H, d), 7.08-7.42(8H,m), 7.79-7.83(2H,m).
5-Chloro-2-isopropoxy - [1,1';2',1'']terphenyl-3-carboxylic acid ethyl ester	0.77-1.1(6H, br.s), 1.34(3H,t), 4.14(1H,m), 4.32(2H,q), 6.58(1H,d), 7.11-7.43(8H,m), 7.85(1H,d), 7.90(1H,s).

### GENERAL PROCEDURE B - Mitsunobu reaction

#### 5 5-Chloro-2-phenethyloxy-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester

A mixture of 5-chloro-2-hydroxy-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester(100 mg, 0.28 mmol), phenethyl alcohol (31 mg, 0.25 mmol), triphenyl phosphine( 74 mg, 0.28 mmol), diisopropyl azodicarboxylate (57 mg, 0.28 mmol) in THF (6 ml) was stirred at room temperature overnight. The mixture was then poured into water and extracted with ether, the organic layers were dried over MgSO<sub>4</sub> and evaporated. The residue was chromatographed through an SPE column using iso-hexane to yield the title compound (95mg, 80%) as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.32(3H,t), 2.74(2H,t), 3.41-3.92(2H, br. d), 4.30(2H,q), 6.54(1H,d), 6.93-7.90(15H, m).

15

### GENERAL PROCEDURE C - ester deprotection

#### Example 27: 5-Chloro-2-(3-methyl-butoxy)-[1,1';2',1'']terphenyl-3"-carboxylic acid

20 5-Chloro-2-(3-methyl-butoxy)-[1,1';2',1'']terphenyl-3"-carboxylic acid ethyl ester(45mg,0.106 mmol) and NaOH (excess) were heated at 60°C in ethanol (3 ml) for 2 hrs. The mixture was then cooled to room temperature, diluted with water , acidified with HCl (1M solution) and extracted with ethyl acetate.The combined extracts were dried (MgSO<sub>4</sub>) and evaporated to yeld the title compound (41 mg, 98%) as a white solid.

25 <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 0.78(6H,d), 1.35(2H,m), 1.44-1.49(1H,m), 3.2-3.7(2H,br.s), 6.61(1H,d), 7.14-7.43(8H,m), 7.91(1H,d), 8.02(1H,s).

LC/MS R<sub>t</sub>=4.13 min. m/z [MH<sup>+</sup>] 393, 395

30 The following Examples 28-42 were prepared from the appropriate ester by methods analogous to General Procedure C. <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> solution.

EXAMPLE	COMPOUND NAME	LC/MS	<sup>1</sup> H NMR
28	5-Chloro-2-(4-fluoro-benzyloxy) - [1,1';2',1'']terphenyl- 3''carboxylic acid	R <sub>t</sub> =3.97 min. [MH <sup>-</sup> ] 431,433	4.52-4.82 (2H,br.d), 6.61(1H,d), 6.92- 7.90(14H, m).
29	5-Chloro-2-(2,4-difluoro-benzyloxy) -[1,1';2',1''] terphenyl-3''-carboxylic acid	R <sub>t</sub> =3.99 min. [MH <sup>-</sup> ] 449,451	4.52-4.80 (2H,br.s), 6.67 (1H,d), 6.69- 7.50(11H,m),7.90(1H, s),7.93(1H,s)
30	5-Chloro-2-(4-chloro-benzyloxy)-[1,1';2',1''] terphenyl-3''carboxylic acid	R <sub>t</sub> =4.12 min. [MH <sup>-</sup> ] 447,449	4.42-4.78(2H,br.d), 6.59 (1H,d), 6.90(1H,d), 7.12- 7.92(13H,m).
31	5-Chloro-2-(2-fluoro-4-chloro-benzyloxy) -[1,1';2',1''] terphenyl-3''carboxylic	R <sub>t</sub> =4.15 min. [MH <sup>-</sup> ] 465,467	4.45-4.81(2H,br.s), 6.64 (1H,d),6.80(1H,t), 7.0(2H,d), 7.14- 7.93(10H, m).
32	5-Chloro-2-(4-isobutoxy)- [1,1',2',1''] terphenyl-3''- carboxylic acid	R <sub>t</sub> =4.05 min. [MH <sup>-</sup> ] 379,381	1.75-1.85(1H,m), 3.39(2H, br. s), 6.64(1H, d), 7.06-7.43 (8H, m), 7.90(1H, d), 7.99(1H, s)
33	5-Chloro-2-(pyridin-2-ylmethoxy) -[1,1';2',1''] terphenyl-3''carboxylic acid	R <sub>t</sub> =3.61 min. [MH <sup>+</sup> ] 416,418	4.61(1H,br.s), 4.87(1H,br.s), 6.61(1H,d), 6.88(1H,d), 7.13- 7.91(12H, m), 8.51(1H, br. s).
34	5-Chloro-2-(pyridin-4-ylmethoxy) -[1,1';2',1''] terphenyl-3''carboxylic acid	R <sub>t</sub> =3.37 min. [MH <sup>+</sup> ] 416,418	
35	5-Chloro-2-(pyridin-3-ylmethoxy) -[1,1';2',1''] terphenyl-3''carboxylic acid	R <sub>t</sub> =3.47 min. [MH <sup>+</sup> ] 416,418	4.19(1H,br. s), 4.79(1H,br.s), 6.62(1H,d), 7.06- 7.88(12H, m) ,8.35(1H,br. s) 8.50(1H, br. s).

36	5-Chloro-2-cyclohexylmethoxy - [1,1';2',1'']terphenyl-3"carboxylic acid	R <sub>t</sub> =4.33 min. [MH <sup>+</sup> ] 421	0.74-1.60(11H, br. m), 3.38(2H,br.s), 6.63(1H,d), 7.08-7.43 (8H,m), 7.91(1H,d), 8.02(1H,s).
37	5-Chloro-2-(thiophen-3-ylmethoxy) -[1,1';2',1''] terphenyl-3"carboxylic acid	R <sub>t</sub> =3.91 min. [MH <sup>+</sup> ] 419,421	4.55-4.85(2H,br.d), 6.66(1H,d) , 6.76(1H, d), 6.87 (1H, s), 7.12-7.92(11H, m).
38	5-Chloro-2-(thiophen-2-ylmethoxy) -[1,1';2',1''] terphenyl-3"carboxylic acid	R <sub>t</sub> =3.89 min. [MH <sup>+</sup> ] 419,420	4.84(2H,br.s), 6.73 (1H,d), 6.79-7.92(13H, m).
39	5-Chloro-2-cyclopentylmethoxy - [1,1';2',1'']terphenyl-3"carboxylic acid	R <sub>t</sub> =4.22 min. [MH <sup>+</sup> ] 405,407	0.83-1.62(8H, br. m), 2.07(1H,m), 3.51 (2H,br.s), 6.65 (1H,d), 7.06-7.44 (8H,m), 7.90 (1H,d), 7.99(1H,s),
40	5-Chloro-2-propoxy [1,1';2',1''] terphenyl-3"carboxylic acid	R <sub>t</sub> =3.92 min. [MH <sup>+</sup> ] 365,367	0.77(3H,t), 1.50 (2H,m), 3.30-3.70(2H, br.d), 6.61(1H, d), 7.13-7.44(8H,m), 7.90 (1H,s), 8.00(1H,s).
41	2-Butoxy-5-chloro-[1,1';2',1''] terphenyl-3"carboxylic acid	R <sub>t</sub> =4.03 min. [MH <sup>+</sup> ] 379,381	0.81(3H,t), 1.16-1.25 (2H,m),1.42-1.49(2H,m), 3.29-3.75 (2H, br.s), 6.61(1H, d), 7.12-7.45(8H,m), 7.91(1H,s), 8.02(1H,s).
42	5-Chloro-2-isopropoxy - [1,1';2',1''] terphenyl-3"carboxylic acid	R <sub>t</sub> =3.87 min. [MH <sup>+</sup> ] 365,367	0.73-0.93(6H, br.s), 4.14(1H,m), 6.81(1H,d), 7.16-7.46(9H,m), 7.77(1H,br. s),

**Example 43: 5-Chloro-2-isobutoxy-[1,1';2',1'']terphenyl-2"-carboxylic acid**

**a) 2'-Bromo-biphenyl-2-carboxylic acid ethyl ester**

- 5 Prepared using the same conditions for the synthesis of 2'-bromo-biphenyl-3-carboxylic acid ethyl ester substituting 3-ethoxycarbonylphenyl boronic acid with 2-ethoxycarbonylphenylphenyl boronic acid.



$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.01 (3H, t,  $J=7\text{Hz}$ ), 4.10 (2H, m), 7.19-7.26 (3H, m), 7.33 (1H, t,  $J=7\text{Hz}$ ), 7.48 (1H, t,  $J=7\text{Hz}$ ), 7.55-7.62 (2H, m), 8.04 (1H, d,  $J=8\text{Hz}$ ).

**b) 5-Chloro-2-hydroxy-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester**

- 5 Prepared using the same conditions used for the synthesis of 5-chloro-2-hydroxy-[1,1';2',1'']terphenyl-3''-carboxylic acid ethyl ester except 2-benzyloxy-5-chloro-[1,1';2,2'']terphenyl-2''-carboxylic acid ethyl ester was used instead of 2-benzyloxy-5-chloro-[1,1';2,2'']terphenyl-3''-carboxylic acid ethyl ester.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.24 (3H, t), 4.23 (2H, q), 6.59 (1H, d), 7.04-7.47 (9H, m), 7.82 (1H, dd).

10

**c) 5-Chloro-2-isobutoxy-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester**

Prepared as in procedure A from 5-chloro-2-hydroxy-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester and 1-bromo-2-methyl-propane.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.85 (6H, br. s), 1.04 (3H, t), 1.91 (1H, m), 3.49 (2H, br. s), 4.07 (2H, br. m),  
15 6.63 (1H, d), 7.03-7.37 (9H, m), 7.71 (1H, d).

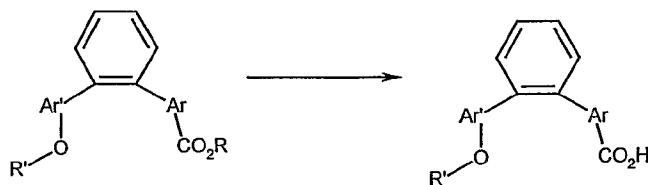
**d) 5-Chloro-2-isobutoxy-[1,1';2',1'']terphenyl-2''-carboxylic acid**

Prepared as in procedure C from 5-chloro-2-isobutoxy-[1,1';2',1'']terphenyl-2''-carboxylic acid ethyl ester.

- 20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.78 (6H, br. t), 1.88 (1H, m), 3.49 (2H, br. d), 6.63 (1H, d), 7.07-7.41 (9H, m), 7.79 (1H, d). LC/MS  $R_t=3.91(100\%)$   $[\text{M}^-]$   $m/z$  379, 381.

**GENERAL PROCEDURE D - Standard Hydrolysis Procedure**

25

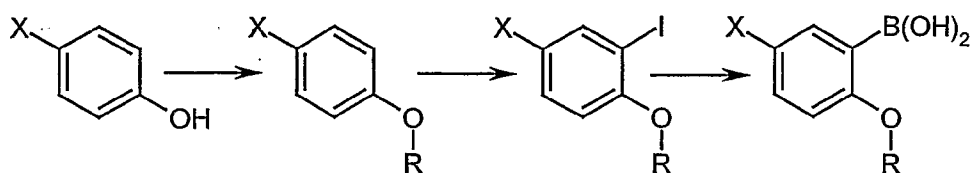


30

The ester (0.5mmol) was dissolved in methanol or ethanol (2ml) and 2M sodium hydroxide (1ml) added. The mixture was stirred at from room temperature to reflux for from 30minutes to 20 hours until the reaction was complete by tlc. The solution was diluted with  
water then extracted with isohexane or diethyl ether and acidified to pH4 with either  
hydrochloric acid or acetic acid. The mixture was extracted with diethyl ether or  
dichloromethane. The organic solution was dried over magnesium sulphate and  
evaporated to give the title compound.

35

**GENERAL PROCEDURE E – Preparation of boronic acid intermediates**

E(i) 4-(Benzyloxy)benzotrifluoride

A solution of 4-hydroxybenzotrifluoride (8.55g, 52.78mmol) in acetone (200ml) was treated with benzyl bromide (9.87g, 6.86ml, 58.05mmol) and potassium carbonate (10.94g, 79.16mmol). The mixture was stirred and heated to reflux under nitrogen for 3h. After cooling, diethyl ether (400ml) and water (400ml) were added and the aqueous phase re-extracted with diethyl ether (100ml). The combined organic layers were washed with water, dried ( $\text{MgSO}_4$ ) and the solvent removed in vacuo to leave the title compound as a white solid. (12.71g, 95%)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 5.11 (2H, s), 7.03 (2H, d,  $J = 9\text{Hz}$ ), 7.34-7.44 (5H, m), 7.55 (2H, d,  $J = 9\text{Hz}$ ).

E(ii) 2-Benzyloxy-5-(trifluoromethyl)iodobenzene

A solution of 4-(benzyloxy)benzotrifluoride (12.71g, 50.4mmol) in acetonitrile (300ml) was stirred under nitrogen and 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (17.75g, 50.4mmol) and iodine (6.4g, 25.2mmol) added. The mixture was stirred at room temperature for 88h. The solvent was evaporated and the residue partitioned between ethyl acetate (400ml) and water (400ml). The organic layer was washed with water, dried ( $\text{MgSO}_4$ ) and evaporated to an orange oil which was purified by flash chromatography (silica gel, 5% ethyl acetate: isohexane) to give the title compound as an orange oil (15.07g, 79%)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 5.21 (2H, s), 6.89 (1H, d  $J = 9\text{Hz}$ ), 7.32-7.55 (6H, m), 8.04 (1H, d,  $J = 2\text{Hz}$ ).

E(iii) 2-Benzyloxy-5-(trifluoromethyl)benzeneboronic acid

A solution of 4-benzyloxy-3-iodobenzotrifluoride (15.07g, 39.85mmol) in tetrahydrofuran (200ml) was cooled to  $-40^\circ\text{C}$  with stirring under nitrogen. 2M isopropylmagnesium chloride in diethyl ether (39.85ml, 79.7mmol) was added dropwise and the mixture stirred at  $-40^\circ\text{C}$  for 40 minutes, then cooled to  $-75^\circ\text{C}$ . Trimethyl borate (8.3g, 9.2ml, 79.7mmol) was added at  $-75^\circ\text{C}$  over 10 minutes and the reaction stirred and allowed to reach  $0^\circ\text{C}$  over 1h. 1M hydrochloric acid (200ml) was added and the mixture stirred vigorously for 1h. The layers were separated and the aqueous layer extracted with diethyl ether (100ml). The combined organic layers were washed with water, dried ( $\text{MgSO}_4$ ) and evaporated. The residue was flash chromatographed (silica gel, 5-20% ethyl acetate: isohexane) to give the title compound as a white solid. (7.71g, 65%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 5.20 (2H, s), 5.79 (2H, s), 7.05 (1H, d,  $J = 9\text{Hz}$ ), 7.39-7.44 (5H, m), 7.68 (1H, dd  $J = 2\text{Hz}$ ,  $J = 9\text{Hz}$ ), 8.15 (1H, d,  $J = 2\text{Hz}$ ).

The following intermediates were prepared using analogous procedures.

4-[(4-Fluorobenzyl)oxy]benzotrifluoride

Prepared by general procedure E(i) but using 4-fluorobenzyl bromide instead of benzyl bromide.

- 5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ : 5.07 (2H, s), 7.02 (2H, d,  $J = 9\text{Hz}$ ), 7.07-7.11 (2H, m), 7.39-7.42 (2H, m), 7.52 (2H, d,  $J = 9\text{Hz}$ )

2-[(4-Fluorobenzyl)oxy]-5-trifluoromethyliodobenzene

Prepared by general procedure E(ii) but using 4-[(4-fluorobenzyl)oxy]benzotrifluoride instead of 4-(benzyloxy)benzotrifluoride.

- 10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 5.16 (2H, s), 6.88 (1H, d,  $J = 9\text{Hz}$ ), 7.08-7.13 (2H, m), 7.44-7.48 (2H, m), 7.54-7.57 (1H, dd,  $J = 2\text{Hz}$ ,  $J = 9\text{Hz}$ ), 8.04 (1H, d,  $J = 2\text{Hz}$ ).

2-[(4-Fluorobenzyl)oxy]-5-trifluoromethylbenzeneboronic acid

- 15 Prepared by general procedure E(iii) but using 4-[(4-fluorobenzyl)oxy]-3-iodobenzotrifluoride instead of 4-benzyloxy-3-iodobenzotrifluoride.

$^1\text{H}$  NMR ( $d_6\text{DMSO}$ )  $\delta$  5.22 (2H, s), 7.20-7.26 (3H, m), 7.54-7.58 (2H, m), 7.71 (1H, d,  $J = 9\text{Hz}$ ), 7.75 (1H, s), 8.03 (2H, s).

4-[(2,4-Difluorobenzyl)oxy]benzotrifluoride

Prepared by general procedure E(i) but using 2,4-difluorobenzyl bromide instead of benzyl bromide.

- 20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.12 (2H, s), 6.89 (2H, dt,  $J = 2\text{Hz}$ ,  $J = 9\text{Hz}$ ), 7.02-7.05 (2H, d,  $J = 9\text{Hz}$ ), 7.33-7.49 (1H, q,  $J = 8\text{Hz}$ ,  $J = 15\text{Hz}$ ), 7.56 (2H, d,  $J = 9\text{Hz}$ )

25

2-[(2,4-Difluorobenzyl)oxy]-5-trifluoromethyliodobenzene

Prepared by general procedure E(ii) but using 4-[(2,4-difluorobenzyl)oxy]benzotrifluoride instead of 4-(benzyloxy)benzotrifluoride.

- 30  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ : 5.21 (2H, s), 6.84-6.95 (3H, m), 7.55-7.65 (2H, m), 8.04 (1H, s)

30

2-[(2,4-Difluorobenzyl)oxy]-5-trifluoromethylbenzeneboronic acid

Prepared by general procedure E(iii) but using 4-[(2,4-difluorobenzyl)oxy]-3-iodobenzotrifluoride instead of 4-benzyloxy-3-iodobenzotrifluoride.

- 35  $^1\text{H}$  NMR ( $d_6\text{DMSO}$ )  $\delta$  5.26 (2H, s), 7.16 (1H, dt,  $J = 2\text{Hz}$ ,  $J = 9\text{Hz}$ ), 7.27 (1H, d,  $J = 9\text{Hz}$ ), 7.33 (1H, dt,  $J = 2\text{Hz}$ ,  $J = 9\text{Hz}$ ), 7.68-7.75 (3H, m), 8.01 (2H, s).

35

2-Benzyloxy-5-bromoiodobenzene.

Prepared as general procedure E(i) from 2-iodo-4-bromophenol

- 40  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.10(2H, s), 6.69(1H, d,  $J=9\text{Hz}$ ), 7.23-7.46(6H, m), 7.88(1H,s).

40

2-Benzyloxy-5-bromobenzeneboronic acid

Prepared as general procedure E(iii) from 2-benzyloxy-5-bromoiodobenzene.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.12(2H, s), 5.78(2H, s), 6.58(1H, d,  $J=9\text{Hz}$ ), 7.34-7.39(5H, m), 7.40(1H, d,  $J=9\text{Hz}$ ), 7.95(1H, s).  
LC/MS:  $R_t = 3.44$  [M-H] 305, 307 (1Br)

5 2-(4-Fluorobenzyl)oxy-5-bromiodobenzene

Prepared as general procedure E(i) from 2-iodo-4-bromophenol.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.06(2H, s), 6.69(1H, d,  $J=9\text{Hz}$ ), 7.07-7.10(2H, m), 7.35-7.45(3H, m), 7.89(1H, s).

10 2-(4-Fluorobenzyl)oxy-5-bromobenzenboronic acid

Prepared as general procedure E(iii) from 2-(4-fluorobenzyl)oxy-5-bromiodobenzene.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.07(2H, s), 5.83(2H, s), 6.84(1H, d,  $J=9\text{Hz}$ ), 7.10(2H, m), 7.37(2H, m), 7.50(1H, d,  $J=9\text{Hz}$ ), 7.95(1H, s).

15 2-(2,4-Difluorobenzyl)oxy-5-bromiodobenzene

Prepared as general procedure E(i) from 2-iodo-4-bromophenol.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.12(2H, s), 6.74-6.95(3H, m), 7.40(1H, d,  $J=9\text{Hz}$ ), 7.57-7.63(1H, m), 7.90(1H, s).

20 2-(2,4-Difluorobenzyl)oxy-5-bromobenzenboronic acid

Prepared as general procedure E(iii) from 2-(2,4-difluorobenzyl)oxy-5-bromiodobenzene.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.14(2H, s), 5.77(2H, br s), 6.86-6.95(3H, m), 7.36-7.42(1H, m), 7.52(1H, d,  $J=9\text{Hz}$ ), 7.95(1H, s).

25 2-[(4-Fluorobenzyl)oxy]-5-chloriodobenzene

Prepared as general procedure E(i) from 2-iodo-5-chlorophenol.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.08(2H, s), 6.75(1H, d,  $J=8\text{Hz}$ ), 7.06(1H, d,  $J=8\text{Hz}$ ), 7.07(1H, d,  $J=8\text{Hz}$ ), 7.23(1H, s), 7.43-7.46(2H, m), 7.76(1H, s).

30 2-[(4-Fluorobenzyl)oxy]-5-chlorobenzenboronic acid

Prepared as general procedure E(iii) from 2-[(4-fluorobenzyl)oxy]-5-chloriodobenzene

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.07(2H, s), 6.89(1H, d,  $J=8\text{Hz}$ ), 7.09(2H, m), 7.35-7.40(3H, m), 7.81(1H, s).

35 Ethyl 2-bromo-4-chlorobenzoate

A mixture of 2-bromo-4-chlorobenzoic acid (235mg, 1mmol) and thionyl chloride (238mg, 146ul, 2mmol) in toluene (5ml) was heated at  $90^\circ\text{C}$  for 1 hour. The reaction mixture was cooled and the solvent evaporated. The residue was dissolved in THF (1ml) and treated with ethanol (1ml). The solution was evaporated to dryness leaving the title

40 compound as a yellow oil 263mg 100%

NMR ( $\text{CDCl}_3$ ):  $\delta$ : 1.41(3H, t,  $J=7\text{Hz}$ ), 4.40(2H, q,  $J=7\text{Hz}$ ), 7.28-7.32(1H, m), 7.57-7.60(1H, m), 7.90(1H, s).

Ethyl 2-bromo-5-chlorobenzoate

A solution of 2-bromo-5-chlorobenzoic acid in ethanol (10ml) and sulphuric acid (0.5ml) was refluxed for 20 hours then cooled and evaporated. The residue was dissolved in diethyl ether/water and the organic layer dried (magnesium sulphate) and evaporated to give 516mg of light brown oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.41 (3H, t), 4.40 (2H, q), 7.30 (1H, dd), 7.58, (1H, d), 7.65 (1H, d).

Ethyl 3-bromo-5-fluorobenzoate

Sulphuric acid (0.5 mL) was added to a stirring solution of 3-bromo-5-fluorobenzoic acid (473 mgs, 2.16 mmol) in ethanol (10 mL) and refluxed for 17 hours. The reaction mixture was cooled to room temperature and diluted with diethyl ether and water. The ether layer was washed with 5% sodium hydrogen carbonate solution, dried over magnesium sulphate and evaporated to dryness to give the title compound as a brown oil. (506 mg).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.40 (3H, t, J=7Hz), 4.39 (2H, q, J=7Hz), 7.43 (1H, td, J=2Hz, J=8Hz), 7.67 (1H, dd, J=2Hz, J=8Hz), 7.98 (1H, s).

t-Butyl 3-bromo-5-iodobenzoate

A mixture of 3-bromo-5-iodobenzoic acid (50g, 153mmol), 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (30.8g, 153mmol), 4-dimethylaminopyridine (18.6g, 153mmol) and t-butanol (69.4g, 90ml, 153mmol) in dichloromethane (500ml) was stirred at room temperature overnight. The reaction mixture was washed with 2M HCl and saturated NaHCO<sub>3</sub>. The organic phase was dried and evaporated to give the title compound as a light brown solid (48g; 85%).

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ: 1.58(9H, s), 7.99(1H, s), 8.05(1H, s), 8.22(1H, s).

t-Butyl 3-bromo-5-cyanobenzoate

A mixture of t-butyl 3-bromo-5-iodobenzoate (1.91g, 5mmol), zinc cyanide (585mg, 5mmol), and tetrakis(triphenylphosphine)palladium(0) (300mg, 5mol%) in dimethylformamide (20ml) was heated at 80°C for 2 hours. The solvent was evaporated. The residue was dissolved in ethyl acetate (20ml) and washed with water and brine. The organic phase was dried and evaporated. Chromatography with ethyl acetate/hexane (1:4) gave the title compound as a colourless oil (1.02g, 73%).

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.60(9H, s), 7.92(1H, s), 8.18(1H, s), 8.32(1H, s).

Ethyl 3-bromo-5-nitrobenzoate

Thionyl chloride (15.7g, 120mmol) was added to a solution of 3-bromo-5-nitrobenzoic acid in toluene (100ml). The mixture was refluxed for 6 hours. The solvent was evaporated and the residue dissolved in dry tetrahydrofuran (50ml), ethanol (10ml) was added and the mixture stirred at room temperature for 30 mins. The solvent was evaporated and the residue chromatographed in dichloromethane to give the title compound as an off-white solid (13g, 79%).

<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.44(3H, t, J=7Hz), 4.45(2H, q, J=7Hz), 8.48(1H, s), 8.54(1H, s), 8.78(1H, s).

Ethyl 3-amino-5-bromobenzoate

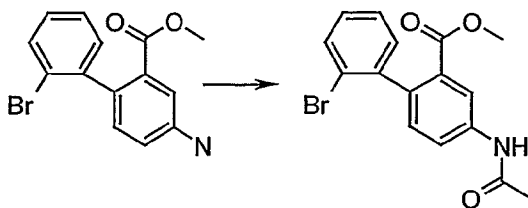
A solution of ethyl 3-bromo-5-nitrobenzoate (4.4g, 16mmol) and tin(II) chloride (40g, 170mmol) in ethanol (125ml) was heated at 80° C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated. The residue was suspended in ethyl acetate (250ml) and washed with 2M NaOH (2x250ml). The organic phase was washed with water, dried and evaporated to give the title compound as a yellow solid (3.6g, 92%)  
<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.37(3H, t, J=7Hz), 3.84(2H, br s), 4.34(2H, q, J=7Hz), 6.98(1H, s), 7.25(1H, s), 7.52(1H, s).

Ethyl 3-bromo-5-[(4-chlorobutanoyl)amino]benzoate

4-Chlorobutyryl chloride (636mg, 505μl, 4.5mmol) was added to a solution of ethyl 3-amino-5-bromobenzoate (1.0g, 4.1mmol) and triethylamine (455mg, 630ul, 4.5mmol) in dichloromethane (25ml) at 0°C. After complete addition the reaction mixture was stirred at room temperature for 30 minutes, then diluted with ethyl acetate (50ml). The solution was washed with 2M HCl, saturated NaHCO<sub>3</sub>, water and brine. The organic phase was dried and evaporated to give the title compound as a pale yellow solid (1.35g, 94%)  
<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.26(3H, t, J=7Hz), 2.20(2H, quintet, J=7Hz), 2.60(2H, t, J=7Hz), 3.67(2H, t, J=7Hz), 4.37(2H, q, J=7Hz), 7.53(1H, br s), 7.89-7.90(2H, m), 8.20(1H, s).

Ethyl 3-bromo-5-(2-oxo-1-pyrrolidinyl)benzoate

Sodium hydride, 60% suspension in oil (186mg, 4.65mmol) was added portionwise over 2 mins to a solution of ethyl 3-bromo-5-[(4-chlorobutanoyl)amino]benzoate (1.35g, 3.87mmol) in dry THF (50ml) under nitrogen. The reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched by the careful addition of water (25ml). Diethyl ether (50ml) was added. The organic phase was washed with water, dried and evaporated to give the title compound as a yellow solid (990mg, 82%).  
<sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 1.39(3H, t, J=7Hz), 2.19(2H, quintet, J=7Hz), 2.64(2H, t, J=7Hz), 3.89(2H, t, J=7Hz), 4.38(2H, q, J=7Hz), 7.93(1H, s), 7.99(1H, s), 8.29(1H, s).

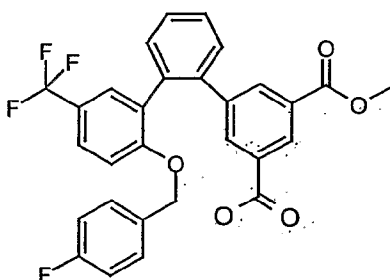
Methyl 4-(acetylamino)-2'-bromo-2-biphenylcarboxylate

Acetyl chloride (70mg, 63μl, 0.89mmol) was added to a solution of methyl 4-amino-2'-bromo-2-biphenylcarboxylate (227mg, 0.74mmol) and triethylamine (90mg, 123ul, 0.89mmol) in diethyl ether (3ml) and stirred at room temperature for 1 hour. The mixture was diluted with ethyl acetate (10ml) and washed with 2M HCl, 5% NaHCO<sub>3</sub>, water and brine. The organic phase was dried and evaporated to leave the title compound as a yellow oil (226mg, 88%).

The following intermediates were prepared using the above method.

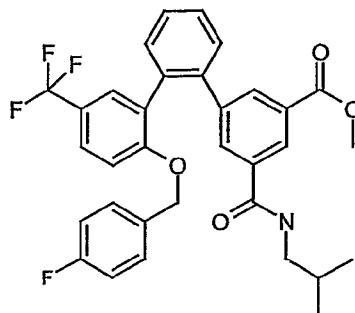
COMPOUND NAME	LCMS or <sup>1</sup> H NMR
Methyl 4-(acetlamino)-2'-bromo-2-biphenylcarboxylate	(CDCl <sub>3</sub> ): 2.20(3H, s), 3.92(3H, s), 7.20-7.99(7H, m).
Methyl 2'-bromo-4-(propanoylamino)-2-biphenylcarboxylate	(CDCl <sub>3</sub> ) 1.26(3H, t, J=7Hz), 2.42(2H, m, J=7Hz), 3.90(3H, s), 7.20-8.03(7H, m).
Methyl 2'-bromo-4-[(2-methylpropanoyl)amino]-2-biphenylcarboxylate	(CDCl <sub>3</sub> ) 1.26(6H, d, J=7Hz), 2.51-2.57(1H, m), 3.91(3H, s), 7.20-8.06(7H, m).

5 **Example 44 2''-{[(4-Fluorophenyl)methyl]oxy}-5'-[(methyloxy)carbonyl]-5''-(trifluoromethyl)-1,1':2,1''-terphenyl-3-carboxylic acid**



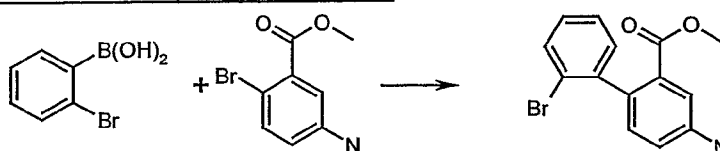
- 10 A solution of dimethyl 2''-{[(4-fluorophenyl)methyl]oxy}-5''-(trifluoromethyl)-1,1':2,1''-terphenyl-3,5-dicarboxylate (1.1g, 2.04mmol) and potassium hydroxide (35mg, 0.62mmol) in methanol (10ml) and water (2ml) was refluxed for 3 hours. After cooling to room temperature, water (30ml) and diethyl ether (10ml) were added. The aqueous phase was acidified with 2M HCl then extracted with ethyl acetate (2x10ml). The combined extracts were dried and evaporated to give the title compound as a colourless solid.
- 15 LCMS: Rt= 4.02 min. [M-H] 523.

**Methyl 2''-{[(4-fluorophenyl)methyl]oxy}-5'-{[(2-methylpropyl)amino]carbonyl}-5''-(trifluoromethyl)-1,1':2,1''-terphenyl-3-carboxylate**



A mixture of 2'-[[[(4-fluorophenyl)methyl]oxy]-5-[(methyloxy)carbonyl]-5''-(trifluoromethyl)-1,1':2',1''-terphenyl-3-carboxylic acid (90mg, 0.17mmol), 4-methylmorpholine (34mg, 45 $\mu$ l, 0.34mmol), 1-hydroxybenzotriazole hydrate (30mg, 0.2mmol), 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (38mg, 0.2mmol), and isobutylamine (25mg, 34 $\mu$ l, 0.34mmol) in dichloromethane (3ml) was stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate (10ml), then washed with saturated NaHCO<sub>3</sub>, 2M HCl, water and brine. The organic phase was dried and evaporated. The residue was purified by chromatography in ethyl acetate/hexane (1:9 – 1:4) to give the title compound as a colourless solid (51mg, 50%). LCMS: Rt= 4.10 min. [M+H] 580

Methyl 4-amino-2'-bromo-2-biphenylcarboxylate



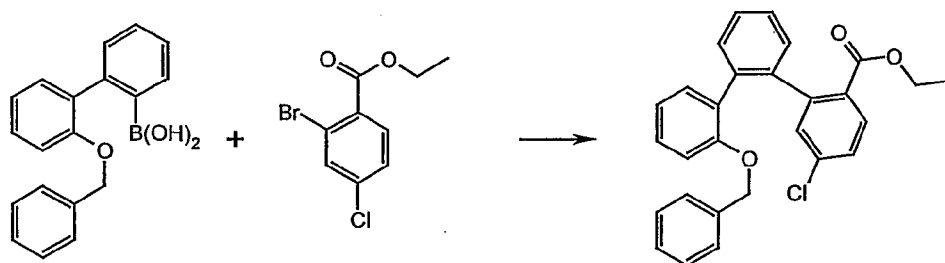
A mixture of 2-bromophenyl boronic acid (600 mg, 3.0 mmol), methyl 5-amino-2-bromobenzoate (1.5g, 6.5 mmol), potassium carbonate (2.07g, 15 mmol) and tetrakis(triphenylphosphine)palladium (0) (345mg, 5mol%) in 1:1 toluene/ethanol (20 ml) was stirred and heated at 90°C under nitrogen for 12 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was chromatographed with dichloromethane/iso-hexane (1:2 -> 1:1) to yield the title compound as a pale yellow gum. (682 mg, 74%).

The following intermediates were prepared using the above method.

COMPOUND NAME	LCMS / <sup>1</sup> H NMR
Methyl 4-amino-2'-bromo-2-biphenylcarboxylate	CDCl <sub>3</sub> :3.85(3H, s), 6.80(1H, d), 6.97-7.33(5H, m), 7.57(1H, d).
t-Butyl 2'-bromo-5-cyano-3-biphenylcarboxylate	Rt = 3.99 min [M+H <sub>2</sub> O] 375,377 (1 Br)
Ethyl 2'-bromo-5-(2-oxo-1-pyrrolidinyl)-3-biphenylcarboxylate	Rt = 3.51 min. [M+H] 388, 390 (1 Br)
Dimethyl 2'-bromo-3,5-biphenyldicarboxylate	Rt = 3.71 min. [M+H] 349,351(1Br)

Ethyl 5-chloro-2'-[(phenylmethyl)oxy]-1,1':2',1''-terphenyl-2-carboxylate



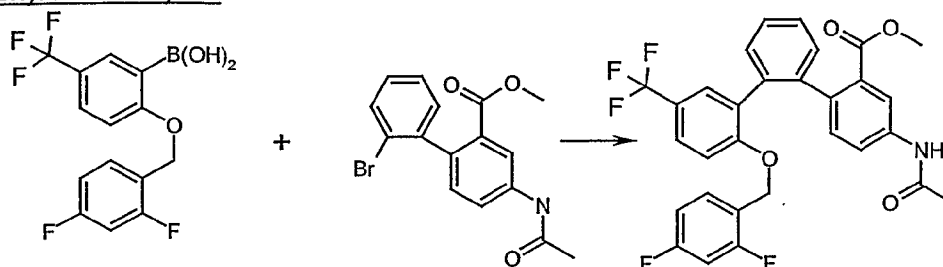


- 5 A mixture of 2'-benzyloxybiphenyl boronic acid (50 mg, 0.16 mmol), ethyl 2-bromo-4-chlorobenzoate (66 mg, 0.25 mmol), potassium carbonate (88 mg, 0.64 mmol) and tetrakis(triphenylphosphine)palladium(0) (10mg, 5mol%) in 1:1 toluene/ethanol (2 ml) was stirred and heated at 90°C under nitrogen for 12 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was chromatographed with ethyl acetate/iso-hexane (1:9) to yield the title compound as a pale yellow gum. (46 mg, 66%).

- 10 The following intermediates were prepared using the above method.

COMPOUND NAME	LCMS/ <sup>1</sup> H NMR
Ethyl 5-chloro-2'-[(phenylmethyl)oxy]-1,1':2',1''-terphenyl-2-carboxylate	(CDCl <sub>3</sub> ) δ: 1.39 (3H, t J=9Hz), 4.38 (2H, q J=9Hz), 4.84-4.93 (2H, br s), 6.75 (2H, m), 6.95-7.45 (12H, m), 7.50-7.70 (1H, m), 7.90-8.03 (1H, m)
Methyl 4-amino-2'-[(phenylmethyl)oxy]-1,1':2',1''-terphenyl-2-carboxylate	(CDCl <sub>3</sub> ) δ: 3.51 (2H, s), 3.63 (3H, s), 4.88-4.91 (2H, br s), 6.54 (br d), 6.75-6.89 (3H, m), 6.97-7.08 (2H, m), 7.10-7.14 (1H, m), 7.23-7.36 (9H, m).
Ethyl 5-fluoro-2'-[(phenylmethyl)oxy]-1,1':2',1''-terphenyl-3-carboxylate	(CDCl <sub>3</sub> ) δ: 1.25 (3H, t), 4.27 (2H, q), 4.55-4.90 (2H, br s), 6.76 (1H, d), 6.90-6.93 (2H, m), 7.03-7.05 (2H, d), 7.16-7.25 (4H, m), 7.41-7.44 (4H, m), 7.50-7.52 (1H, d), 7.63 (1H, s)

Methyl 4-(acetlamino)-2'-{[(2,4-difluorophenyl)methyl]oxy}-5''-(trifluoromethyl)-1,1':2',1''-terphenyl-2-carboxylate



15

A mixture of 2'-[(2,4-difluorobenzyl)oxy]-5-trifluoromethylbenzene boronic acid (66mg, 0.2mmol), methyl 4-(acetlamino)-2-bromo-2-biphenylcarboxylate (110mg, 0.32mmol),

- potassium carbonate (138mg, 1mmol) and tetrakis(triphenylphosphine)palladium(0) (23mg, 5mol%) in 1:1 toluene/ethanol (4 ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was
- 5 chromatographed with ethyl acetate/iso-hexane (2:3) to yield the title compound as a pale yellow gum. (90mg).

The following intermediates were prepared by the above method.

COMPOUND NAME	LCMS / <sup>1</sup> H NMR
Methyl 4-(acetlamino)-2"-{[(2,4-difluorophenyl)methyl]oxy}-5"- (trifluoromethyl)-1,1':2',1"-terphenyl-2-carboxylate.	(CDCl <sub>3</sub> ) 2.05(3H,s), 3.56(3H, s) 4.88-4.90(2H, br s), 6.76-6.79(2H, m), 6.99-7.01(1H, m), 7.26-7.40(4H, m), 7.46-8.00(6H, m)
Methyl 2"-{[(2,4-difluorophenyl)methyl]oxy}-4-(propanoylamino)-5"- (trifluoromethyl)-1,1':2',1"-terphenyl-2-carboxylate.	(CDCl <sub>3</sub> ) 1.21-1.28(3H, m), 2.36-2.41(2H, m), 3.52(3H, s), 4.82-5.03(2H, br s), 6.76-6.79(2H, m), 7.00-7.02(2H, m), 7.26-7.42(6H, m), 7.65-7.99(3H, m).
Methyl 2"-{[(2,4-difluorophenyl)methyl]oxy}-4-[(2-methylpropanoyl)amino]-5"- (trifluoromethyl)-1,1':2',1"-terphenyl-2-carboxylate	(CDCl <sub>3</sub> ) 1.23-1.28(6H, m), 2.49-2.56(1H, m), 3.53-3.58(1H, br s), 4.82-5.03(2H, br s), 6.77-6.79(2H, m), 6.95-7.00(1H, m), 7.20-7.55(6H, m), 7.70-8.02(4H, m).
t-Butyl 5"-bromo-5-cyano-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.38 min [M+H <sub>2</sub> O] 583.
t-Butyl 5"-bromo-5-cyano-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.42 min. [M+H <sub>2</sub> O] 557,559 (1Br)
t-Butyl 5-cyano-2"-[(phenylmethyl)oxy]-5"- (trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.37 min. [M+H <sub>2</sub> O] 547
Ethyl 2"-{[(phenylmethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)-5"- (trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.06 min. [M+H] 560

Dimethyl 2"-[[[(4-fluorophenyl)methyl]oxy]-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3,5-dicarboxylate	(CDCl <sub>3</sub> ) δ: 3.82 (6H, s), 4.45-4.55 (1H, br s), 4.70-4.80 (1H, br s), 6.73 (1H, d, J=8Hz), 6.94 (3H, m), 7.39-7.56 (7H, m), 7.89 (1H, s), 8.48 (1H, m)
Methyl 2"-[(phenylmethyl)oxy]-5-(propanoylamino)-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.04 min [M-H] 532
Ethyl 2"-[[[(4-fluorophenyl)methyl]oxy]-5-(propanoylamino)-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylate	Rt = 3.96 min [M-H] 564
Methyl 2"-[[[(2,4-difluorophenyl)methyl]oxy]-5-(propanoylamino)-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.00 min [M-H] 568

The following compounds were prepared in a similar manner to 2-Benzoyloxy-5-chloro-5"-propionylamino[1,1':2'1"]terphenyl-3"-carboxylic acid ethyl ester (Example 6a):

COMPOUND NAME	LC/MS
Ethyl 5"-chloro-5-[[[(methyloxy)acetyl]amino]-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-3-carboxylate	Rt = 3.97 min [M+H] 528,530
Ethyl 5"-chloro-2"-[(phenylmethyl)oxy]-5-[(2-thienylacetyl)amino]-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.16 min [M+H] 580,582
Ethyl 5"-chloro-2"-[(phenylmethyl)oxy]-5-[[[(phenylmethyl)oxy]acetyl]amino]-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.23 min [M+H] 604,606
Ethyl 4-[[[(1-acetyl-5-piperidiny)carbonyl]amino]-5"-chloro-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-3-carboxylate	Rt = 3.80 min [M+H] 609,611
Ethyl 5"-chloro-5-[(phenylcarbonyl)amino]-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.18 min [M+H] 574,576
Ethyl 5"-chloro-5-[[[(3,5-dimethyl-4-isoxazolyl)carbonyl]amino]-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.09 min [M+H] 579,581
Methyl 5"-chloro-5-[(3-methylbutanoyl)amino]-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.17 min [M+H] 540,542

Methyl 5"-chloro-5-[(N-[(9 <i>H</i> -fluoren-9-ylmethyl)oxy]carbonyl)glycyl)amino]-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-3-carboxylate	Rt = 4.24 min [M-H] 723
Methyl 2"-[(phenylmethyl)oxy]-4-(propanoylamino)-1,1':2',1"-terphenyl-2-carboxylate	Rt = 3.74 min [M-H] 464
Methyl 4-[(2-methylpropanoyl)amino]-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-2-carboxylate	Rt = 3.84 min [M-H] 479

The following Examples 45-65 were prepared from the appropriate ester intermediate by the standard hydrolysis procedure (General Procedure D):

EXAMPLE	COMPOUND NAME	LC/MS	H NMR
45	5-Chloro-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-2-carboxylic acid	Rt = 3.92 min [M-H] 413 (1 Cl)	(CDCl <sub>3</sub> ) 4.89-4.92 (2H, br s), 6.71(1H, d, J=9Hz), 6.93-7.68(15H, m).
46	4-(Methoxy)-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-2-carboxylic acid	Rt=3.69 min [M-H] 409	(d <sub>6</sub> -DMSO) 3.72(3H, s), 5.02(2H, br s), 6.72-7.32(15H, m), 12.50(1H, br s).
47	2"-[(2,4-Difluorophenyl)methyl]oxy]-4-(propanoylamino)-5"--(trifluoromethyl)-1,1':2',1"-terphenyl-2-carboxylic acid	Rt= 3.69 min [M-H] 554	(CDCl <sub>3</sub> ) 1.24(3H,s, J= 7 Hz), 2.39(2H, q, J=7 Hz), 4.87(2H, br s), 6.74-6.79(3H, m), 7.00-7.02(2H, m), 7.15(1H, br s), 7.26-7.42(5H, m), 7.81(1H, s), 7.82(1H,s).

48	2"-{[(2,4-Difluorophenyl)methyl]oxy}-4-[(2-methylpropanoyl)amino]-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-2-carboxylic acid	Rt = 3.78 min [M-H] = 568	(CDCl <sub>3</sub> ) 1.24(6H, d, J=7Hz), 2.50(1H, m, J= 7Hz), 4.86(2H, br s), 6.75- 6.78(3H, m), 6.95- 7.03(2H, m), 7.23- 7.42(6H, m), 7.84(1H, m), 7.85(1H, d).
49	5-(2-Oxo-1-pyrrolidiny)-2"-[(phenylmethyl)oxy]-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylic acid	Rt = 3.80 min [M-H] 530	(CDCl <sub>3</sub> ) 2.4(2H, m)2.54(2H, t, J= 8Hz), 3.30-3.50(2H, br s)4.60-4.92(2H, br s), 6.77(1H, d, J= 8Hz), 6.98-7.00(2H, m), 7.22-7.26(4H, m), 7.36-7.66(7H, m), 8.30(1H,s).
50	2"-{[(4-Fluorophenyl)methyl]oxy}-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3,5-dicarboxylic acid	Rt = 3.86 min [M-H] 509	(d <sub>6</sub> -DMSO) 4.65(1H, br s), 4.95(1H, br s), 7.05- 7.09(5H, m), 7.41- 7.82(7H, m), 8.28- 8.45(2H. m).
51	2"-{[(4-Fluorophenyl)methyl]oxy}-5-{[(2-methylpropyl)amino]carbonyl}-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylic acid	Rt = 3.97 min [M-H] 564	(CDCl <sub>3</sub> ) 0.92(6H, d, J=6Hz), 1.76-1.83(1H, m), 3.19(2H, br s), 4.61(1H, br s), 4.79(1H, br s), 5.78(1H, br s), 6,78(1H, d, J=8Hz), 6.91-6.99(4H, m), 7.40-7.66(7H, m), 7.95(1H, s), 8.33(1H, s).

52	6-[2'-[(4-Fluorophenyl)methyl]oxy]-5'-(trifluoromethyl)-2-biphenyl]-2-pyrazinecarboxylic acid	Rt = 3.92 min [M+H] 469	(D <sub>4</sub> -MeOD) 4.80(2H, br s), 6.97(2H, t, J= 9Hz) 7.06(3H, t, J=8Hz), 7.43(1H, d, J=8Hz), 7.52(1H, s), 7.56- 7.58(3H, m), 7.82(1H, d, J=8Hz, 8.21(1H, s), 8.98(1H, s).
53	2"-[(4-Fluorophenyl)methyl]oxy]-5-(propanoylamino)-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylic acid	Rt = 3.80 min [M-H] 536	(CDCl <sub>3</sub> ) 1.21 (3H, t), 2.33 (2H, q), 4.60-4.89 (2H, br), 5.30 (1H, s), 6.78 (1H, d), 6.92-7.04 (7H, m), 7.38-7.56 (9H, m), 7.96 (1H, s).
54	2"-[(Phenylmethyl)oxy]-5-(propanoylamino)-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylic acid	Rt = 3.76 min [M-H] 518	(CDCl <sub>3</sub> ) 1.21 (3H, t), 2.32 (2H, q), 4.55-4.98 (2H, br), 6.79 (1H, d), 6.88 (1H, s), 7.04 (2H, d), 7.24- 7.28 (4H, m), 7.41- 7.48 (5H, m), 7.52 (1H, s), 8.03 (1H, s).
55	2"-[(2,4-Difluorophenyl)methyl]oxy]-5-(propanoylamino)-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylic acid	Rt = 3.81 min [M-H] 554	(CDCl <sub>3</sub> ) 1.21 (3H, t), 2.34 (2H, q), 4.73-5.00 (2H, br), 6.75 (2H, m), 6.83 (1H, d), 6.94-6.99 (2H, m), 7.36-7.39 (2H, m), 7.44-7.51 (4H, m), 7.68 (1H, s), 7.90 (1H, s).

56	5"-Chloro-5- {[(methyloxy)acetyl]amino}- 2"-[(phenylmethyl)oxy]- 1,1':2',1"-terphenyl-3- carboxylic acid	Rt = 3.69 min [M+H] 500,502	(CDCl <sub>3</sub> ) 3.48 (3H, s), 3.98 (2H, s), 4.59-4.89 (2H, br), 6.66 (1H, d), 7.03 (2H, d), 7.12 (1H, d), 7.19 (1H, s), 7.23-7.25 (5H, m), 7.42-7.45 (3H, m), 7.59 (1H, d), 8.10 (1H, d).
57	5"-Chloro-2"- [(phenylmethyl)oxy]-5-[(2- thienylacetyl)amino]- 1,1':2',1"-terphenyl-3- carboxylic acid	Rt = 3.95 min [M+H] 552,554	(CDCl <sub>3</sub> ) 3.89 (2H, s), 4.50-4.87 (2H, br), 6.64 (1H, d), 7.00 (3H, d), 7.06-7.11 (3H, m), 7.16 (1H, s), 7.23 (3H, d), 7.32 (2H, s), 7.37-7.44 (3H, m), 7.61 (1H, s), 8.01 (1H, s).
58	5"-Chloro-2"- [(phenylmethyl)oxy]-5- {[(phenylmethyl)oxy]acetyl}a mino)-1,1':2',1"-terphenyl-3- carboxylic acid	Rt = 4.03 min [M+H] 576,578	(CDCl <sub>3</sub> ) 4.06 (2H, s), 4.64 (2H, s), 4.64-4.85 (2H, br), 6.65 (1H, d), 7.02 (2H, d), 7.11 (1H, d), 7.17- 7.23 (4H, m), 7.35- 7.44 (9H, m), 7.56 (1H, s), 7.61 (1H, s), 8.05 (1H, s), 8.16 (1H, s).
59	5-{[(1-Acetyl-4- piperidiny]carbonyl]amino}- 5"-chloro-2"- [(phenylmethyl)oxy]- 1,1':2',1"-terphenyl-3- carboxylic acid	Rt = 3.51 min [M+H] 581,583	(d <sub>6</sub> -DMSO) 1.45-1.61 (2H, m), 1.78 (2H, d), 2.02 (3H, s), 4.02 (2H, broad singlet), 4.84 (2H, s), 6.90 (1H, d), 7.00 (1H, s), 7.12 (2H, d), 7.17 (1H, d), 7.20 (3H, d), 7.30 (1H, d), 7.35-7.42 (3H, m), 7.70 (1H, s), 7.92 (1H, s), 9.37 (1H, s).

60	5"-Chloro-5- [(phenylacetyl)amino]-2"- [(phenylmethyl)oxy]- 1,1':2',1"-terphenyl-3- carboxylic acid	Rt = 3.98 min [M+H] 546,548	(CDCl <sub>3</sub> ) 3.68 (2H, s), 4.45-4.86 (2H, br), 6.62 (1H, d), 6.85 (1H, s), 7.01 (2H, s), 7.10 (1H, d), 7.14 (1H, s), 7.21 (3H, s), 7.28-7.43 (10H, m), 7.58 (1H, s), 7.96 (1H, s).
61	5"-Chloro-5-[(3,5-dimethyl- 4- isoxazolyl)carbonyl]amino}- 2"-[(phenylmethyl)oxy]- 1,1':2',1"-terphenyl-3- carboxylic acid	Rt = 3.84 min [M+H] 551, 553	(CDCl <sub>3</sub> ) 2.43 (3H, s), 2.62 (3H, s), 4.56-4.90 (2H, br), 6.67 (1H, d), 6.98 (1H, s), 7.01 (2H, d), 7.14 (1H, d), 7.21-7.24 (3H, m), 7.36-7.10 (2H, m), 7.46-7.48 (3H, m), 7.70 (1H, s), 8.23 (1H, s).
62	5"-Chloro-5-[(3- methylbutanoyl)amino]-2"- [(phenylmethyl)oxy]- 1,1':2',1"-terphenyl-3- carboxylic acid	Rt = 3.95 min [M+H] 512, 514	(CDCl <sub>3</sub> ) 0.98-1.02 (6H, m), 1.07-1.34 (1H, m), 2.18 (2H, s), 4.56-4.90 (2H, br), 6.65 (1H, d), 6.89 (1H, s), 7.03 (2H, d), 7.11 (1H, d), 7.19 (1H, s), 7.22-7.25 (2H, m), 7.38-7.46 (5H, m), 7.60 (1H, s), 8.07 (1H, s).
63	5"-Chloro-5-(glycylamino)- 2"-[(phenylmethyl)oxy]- 1,1':2',1"-terphenyl-3- carboxylic acid	Rt = 2.91 min [M+H] 485, 487	(d <sub>6</sub> DMSO) 4.65-4.95 (2H, br), 6.92 (1H, d), 7.06-7.09 (3H, m), 7.23-7.27 (2H, m), 7.34-7.47 (5H, m), 7.67 (1H, s), 8.10 (1H, s).

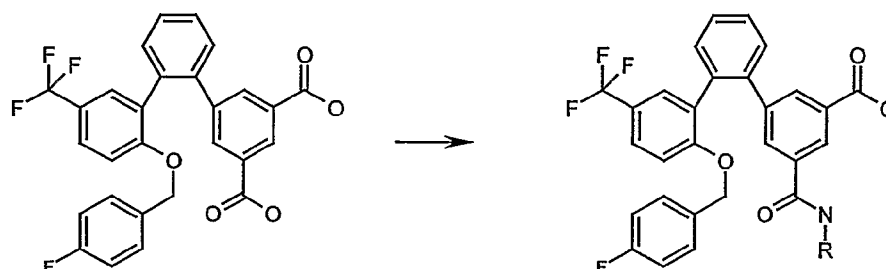


64	2"-[(Phenylmethyl)oxy]-4-(propanoylamino)-1,1':2,1''-terphenyl-2-carboxylic acid	Rt = 3.54 min [M-H] 450	(d <sub>6</sub> -DMSO) 1.07 (3H, t), 2.30 (2H, q), 4.20-5.07 (2H, br), 6.70 (1H, t), 6.79 (1H, d), 6.95 (2H, t), 7.06-7.15 (2H, m), 7.22-7.32 (8H, m), 7.46 (1H, d), 7.91 (1H, s), 9.91 (1H, s), 12.37-12.60 (1H, br).
65	4-[(2-Methylpropanoyl)amino]-2'-[(phenylmethyl)oxy]-1,1':2,1''-terphenyl-2-carboxylic acid	Rt = 3.64 min [M-H] 464	(d <sub>6</sub> -DMSO) 1.08 (6H, d), 5.02 (2H, s), 6.72 (1H, t), 6.79 (1H, d), 6.96 (2H, t), 7.08-7.15 (2H, m), 7.25-7.33 (8H, m), 7.47 (1H, d), 7.94 (1H, s), 9.90 (1H, s), 12.34-12.60 (1H, br).

Examples 66-68 were prepared by cleavage of their t-butyl esters using 25% trifluoroacetic acid in dichloromethane.

EXAMPLE	COMPOUND NAME	LC/MS	<sup>1</sup> H NMR
66	5-Cyano-2"-{[(2,4-difluorophenyl)methyl]oxy}-5''-(trifluoromethyl)-1,1':2,1''-terphenyl-3-carboxylic acid	Rt = 3.99 min [M-H] 508	(CDCl <sub>3</sub> ) 5.16(2H, s), 6.90-7.43(9H, m), 7.72(1H, d, J=9Hz), 7.95(1H, s), 8.37(1H, s), 8.40(1H,s).
67	5''-Bromo-5-cyano-2"-[(phenylmethyl)oxy]-1,1':2,1''-terphenyl-3-carboxylic acid	Rt = 4.03 min [M-H] 482,484 (1 Br)	(CDCl <sub>3</sub> ) 4.60(1H, br s), 4.80(1H, br s), 6.64(1H, d, J = 9Hz), 6.99-7.01(2H, m), 7.27-7.52(10H, m), 8.03( 1H, s), 8.17(1H,s).

68	5-Cyano-2"-[(phenylmethyl)oxy]-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylic acid	Rt = 3.99 [M-H] 472	
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**General Reaction F**

- 5 A mixture of 2"-[(4-fluorophenyl)methyl]oxy}-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3,5-dicarboxylic acid (50mg, 0.1mmol), 4-methylmorpholine (20mg, 22 $\mu$ l, 0.2mmol), 1-hydroxybenzotriazole hydrate (18mg, 0.12mmol), 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (23mg, 0.12mmol), and the amine(0.1mmol) in dichloromethane (3ml) was stirred at room temperature for 2 hours. The mixture was
- 10 diluted with ethyl acetate (10ml), then washed with saturated NaHCO<sub>3</sub>, 2M HCl, water and brine. The organic phase was dried and evaporated. The residue was purified by mass directed preparative LCMS to give the following Examples 69-71:

EXAMPLE	COMPOUND NAME	LC/MS	<sup>1</sup> H NMR
69	5-(Aminocarbonyl)-2"-[(4-fluorophenyl)methyl]oxy}-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylic acid	Rt = 3.60 min [M-H] 508	(CDCl <sub>3</sub> ) 4.65(1H, br s), 4.82(1H, br s), 5.80(1H, br s), 6.05(1H, br s), 6.78(1H, d, J = 9Hz), 6.99-7.02(4H, m), 7.41-7.51(6H, m), 7.71(1H, s), 7.97(1H, s), 8.34(1H, s).
70	2"-[(4-Fluorophenyl)methyl]oxy}-5-[[2-(hydroxyethyl)amino]carbonyl]-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylic acid	Rt = 3.52 min [M-H] 552	(CDCl <sub>3</sub> ) 3.60(2H, br s), 3.86(2H, t, J=4Hz), 4.65(1H, br s), 4.80(1H, br s), 6.71(1H, d, J= 8Hz), 6.89-6.94(3H, m), 7.37-7.49(5H, m), 7.83(1H, s), 7.86(1H, s), 8.45(1H, s).

71	2"-[[[4-Fluorophenyl)methyl]oxy]-5-[[[3-pyridinylmethyl)amino]carbonyl]-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-3-carboxylic acid	Rt = 3.54 min [M+H] 601 [M-H] 599	(CDCl <sub>3</sub> ) 4.57(1H, br s), 4.69(1H, br s), 6.66-6.94(6H, m), 7.26-7.48(6H, m), 7.72-7.74(2H, m), 7.90(1H, s), 8.38(1H, s), 8.40-8.50(1H, br s), 8.65-8.75(1H, br s).
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### Preparation of Intermediates

#### 2'-Bromo-5-chloro-2-[(phenylmethyl)oxy]biphenyl

- 5 A mixture of 2-bromophenylboronic acid (2.01g, 10mmol), 4-chloro-2-iodo-1-[(phenylmethyl)oxy]benzene (3.445g, 10mmol), potassium carbonate (5.52g, 40mmol) and tetrakis(triphenylphosphine)palladium(0) (580mg, 0.5mmol) in 1:1 toluene/ethanol (45ml) was stirred and heated at 90°C under nitrogen for 2 hours when a further 1g (4.98mmol) of 2-bromophenylboronic acid and 0.2g (0.17mmol) of
- 10 tetrakis(triphenylphosphine)palladium(0) were added. The mixture was heated for 6 hours then cooled, diluted with diethyl ether/water and the organic phase separated, dried (magnesium sulphate) and evaporated. The residue was purified by chromatography on silica eluting with ethyl acetate/iso-hexane (1:49) then rechromatographed eluting with dichloromethane/iso-hexane (1:9) to give 2.06g of colourless gum which slowly
- 15 crystallised.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 5.04 (2H, s), 6.92 (1H, d, J=9Hz), 7.18-7.35 (5H, m), 7.66 (1H, dd, J=8Hz, 1Hz).

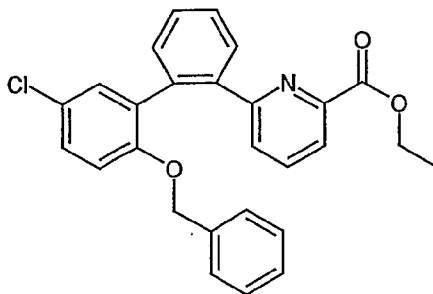
#### {5'-Chloro-2'-[(phenylmethyl)oxy]-2-biphenyl}boronic acid

- 20 1.6M butyllithium in hexanes (16.8ml, 26.88mmol) was added over 10 minutes to a stirred solution of 2'-bromo-5-chloro-2-[(phenylmethyl)oxy]biphenyl (9.29g, 25.56mmol) in tetrahydrofuran (120ml) at -78°C under nitrogen. After stirring for 15 minutes triisopropyl borate (9.61g, 51.12mmol) was added over 2 minutes and the mixture allowed to warm to room temperature. 2M hydrochloric acid (150ml) was added with vigorous stirring for 25
- 25 minutes and the organic phase was separated, dried (magnesium sulphate) and evaporated. The residue was purified by chromatography on silica eluting with ethyl acetate/iso-hexane (1:4) then triturated with iso-hexane to give 5.15g of white solid.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.94-1.98 (2H, m), 2.64-2.74 (4H, m), 4.37 (2H, s), 5.07 (2H, s), 6.90 (1H, d, J=9Hz), 7.15-7.38 (7H, m).

30

#### Ethyl 6-{5'-chloro-2'-[(phenylmethyl)oxy]-2-biphenyl}-2-pyridinecarboxylate

75

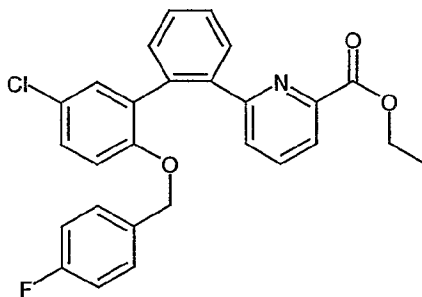


A mixture of {5'-chloro-2'-[(phenylmethyl)oxy]-2-biphenyl}boronic acid (1.32g, 3.9mmol), ethyl 6-bromopicolinate (851mg, 3.7mmol), potassium carbonate (2.76g, 20mmol) and tetrakis(triphenylphosphine)palladium(0) (232mg, 0.2mmol) in 1:1 toluene/ethanol (25ml) was stirred and heated at 90°C under nitrogen for 1.5 hours. After cooling and dilution with diethyl ether/water the organic phase was separated, dried (magnesium sulphate) and evaporated. The residue was chromatographed on silica eluting with ethyl acetate/iso-hexane (3:17) to give 1.37g of white solid. LC/MS t=3.76, [MH<sup>+</sup>] 444.3

Ethyl 6-(5'-chloro-2'-hydroxy-2-biphenyl)-2-pyridinecarboxylate

Ethyl 6-(5'-chloro-2'-[(phenylmethyl)oxy]-2-biphenyl)-2-pyridinecarboxylate (1.22g, 2.75mmol) was dissolved in acetic acid (5ml) and 48% hydrogen bromide in acetic acid (5ml), left at room temperature for 0.5 hours then diluted with diethyl ether/water and basified with potassium carbonate. The organic phase was separated, dried (magnesium sulphate), evaporated and chromatographed on silica eluting with ethyl acetate/iso-hexane (1:3). The product was dissolved in ethanol (20ml), 60% sodium hydride (2mg) added and the solution left at room temperature for 16 hours. The resulting solution was acidified with acetic acid, diluted with water/ether and the organic phase washed with saturated sodium bicarbonate solution, dried (magnesium sulphate), evaporated and chromatographed on silica to give 801mg of colourless gum. LC/MS t=3.33, [MH<sup>+</sup>] 354.3, 356.3

Ethyl 6-(5'-chloro-2'-[(4-fluorophenyl)methyl]oxy)-2-biphenyl)-2-pyridinecarboxylate

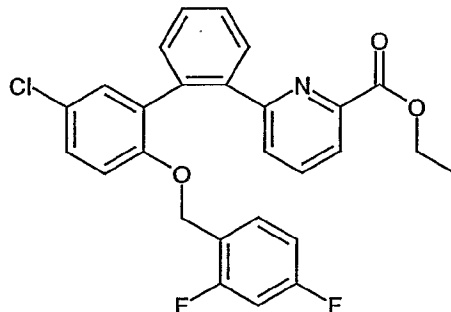


A mixture of ethyl 6-(5'-chloro-2'-hydroxy-2-biphenyl)-2-pyridinecarboxylate (177mg, 0.5mmol), potassium carbonate (138mg, 1mmol) and 4-fluorobenzyl bromide (104mg, 0.55mmol) in acetone (4ml) was stirred and refluxed for 2 hours then cooled, filtered,

evaporated and chromatographed on silica eluting with ethyl acetate/iso-hexane (1:9) to give 190mg of white solid. LC/MS  $t=3.79$ ,  $[MH^+]$  462.3

Ethyl 6-(5'-chloro-2'-[(2,4-difluorophenyl)methyl]oxy)-2-biphenyl)-2-pyridinecarboxylate

5



Prepared in a similar manner to ethyl 6-(5'-chloro-2'-[(4-fluorophenyl)methyl]oxy)-2-biphenyl)-2-pyridinecarboxylate but using 2,4-difluorobenzyl bromide in place of 4-fluorobenzyl bromide. LC/MS  $t=3.82$ ,  $[MH^+]$  480.3

10

2'-Bromo-2'-[(4-fluorophenyl)methyl]oxy)-5-(trifluoromethyl)biphenyl

Prepared as for 2'-bromo-5-chloro-2'-[(phenylmethyl)oxy]biphenyl but using 1'-[(4-fluorophenyl)methyl]oxy)-2-iodo-4-(trifluoromethyl)benzene instead of 4-chloro-2-iodo-1'-[(phenylmethyl)oxy]benzene.

15

$^1H$  NMR ( $CDCl_3$ )  $\delta$ : 5.08 (2H, s), 6.99 (2H, t), 7.04 (1H, d), 7.12-7.36 (5H, m), 7.46 (1H, d), 7.60 (1H, dd), 7.66 (1H, d).

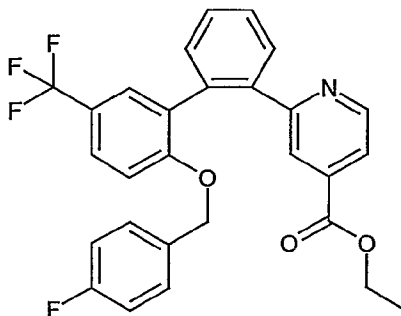
[2'-[(4-Fluorophenyl)methyl]oxy)-5'-(trifluoromethyl)-2-biphenyl]boronic acid

Prepared as for {5'-chloro-2'-[(phenylmethyl)oxy]-2-biphenyl}boronic acid but using 2'-bromo-2'-[(4-fluorophenyl)methyl]oxy)-5-(trifluoromethyl)biphenyl instead of 2'-bromo-5-chloro-2'-[(phenylmethyl)oxy]biphenyl. LC/MS  $t=3.63$ ,  $[MH^-]$  389.0

20

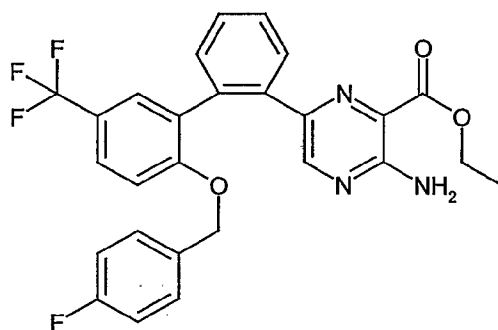
Ethyl 2-[2'-[(4-fluorophenyl)methyl]oxy)-5'-(trifluoromethyl)-2-biphenyl]-4-pyridinecarboxylate

25



A mixture of [2'-{[(4-fluorophenyl)methyl]oxy}-5'-(trifluoromethyl)-2-biphenyl]boronic acid (98mg, 0.25mmol), ethyl 2-bromo-4-pyridinecarboxylate (58mg, 0.25mmol), potassium carbonate (276mg, 2mmol) and tetrakis(triphenylphosphine)palladium(0) (29mg, 0.025mmol) in 1:1 toluene/ethanol (4ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling and dilution with diethyl ether/water the organic phase was separated, dried (magnesium sulphate) and evaporated. The residue was chromatographed on silica eluting with ethyl acetate/iso-hexane (1:9) to give 81mg of colourless gum. LC/MS  $t_r$ =4.10, [MH<sup>+</sup>] 496.1

10 Ethyl 3-amino-6-[2'-{[(4-fluorophenyl)methyl]oxy}-5'-(trifluoromethyl)-2-biphenyl]-2-pyrazinecarboxylate



Prepared as a white solid in a similar manner to ethyl 2-[2'-{[(4-fluorophenyl)methyl]oxy}-5'-(trifluoromethyl)-2-biphenyl]-4-pyridinecarboxylate but using methyl 3-amino-6-bromo-2-pyrazinecarboxylate in place of ethyl 2-bromo-4-pyridinecarboxylate. LC/MS  $t_r$ =3.96, [MH<sup>+</sup>] 512.1

Ethyl 5-(acetylamino)-2-bromobenzoate

20 A mixture of 5-(acetylamino)-2-bromobenzoic acid (2.58g, 10mmol), 1-hydroxybenzotriazole (1.68g, 11mmol), dimethylaminopyridine (1.22g, 10mmol) and 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (2.20g, 11.5mmol) in dichloromethane/ethanol (5:1, 30ml) was stirred at room temperature for 2 hours then washed with saturated sodium bicarbonate solution, dried (magnesium sulphate) and chromatographed on silica eluting with ethyl acetate/iso-hexane (2:3) to give 2.18g of white solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.40 (3H, t), 2.19 (3H, s), 4.39 (2H, q), 7.27 (1H, br s), 7.58 (1H, d), 7.64 (1H, dd), 7.84 (1H, d).

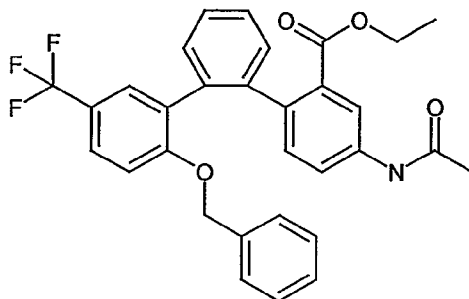
30 Ethyl 4-(acetylamino)-2'-bromo-2-biphenylcarboxylate

A mixture of 2-bromophenylboronic acid (1.61g, 8.0 mmol), ethyl 5-(acetylamino)-2-bromobenzoate (2.15g, 7.5 mmol), potassium carbonate (5.52g, 40 mmol) and tetrakis(triphenylphosphine)palladium(0) (869mg, 0.75mmol) in 1:1 toluene/ethanol (40 ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried (MgSO<sub>4</sub>) and evaporated

to dryness. The residue was chromatographed with ethyl acetate/iso-hexane (2:3) to yield 1.33g of the title compound as a white foam.

LC/MS t=3.26, [MH<sup>+</sup>] 364.0

5 Ethyl 4-(acetylamino)-2'-[(phenylmethyl)oxy]-5''-(trifluoromethyl)-1,1':2',1''-terphenyl-2-carboxylate



10 A mixture of [2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]boronic acid (118mg, 0.4 mmol), ethyl 4-(acetylamino)-2'-bromo-2-biphenylcarboxylate (121mg, 0.33 mmol), potassium carbonate (414mg, 3 mmol) and tetrakis(triphenylphosphine)palladium(0) (39mg, 0.033mmol) in 1:1 toluene/ethanol (5 ml) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with diethyl ether and water and the organic phase dried (MgSO<sub>4</sub>) and evaporated to dryness. The residue was

15 chromatographed with ethyl acetate/iso-hexane (1:2) to yield 121mg of the title compound as a colourless gum.

LC/MS t=3.88, [MH<sup>-</sup>] 532.2

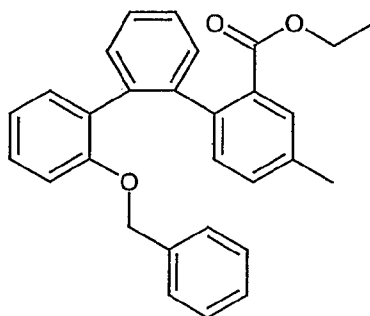
20 The following intermediates were prepared by a similar route to ethyl 4-(acetylamino)-2'-[(phenylmethyl)oxy]-5''-(trifluoromethyl)-1,1':2',1''-terphenyl-2-carboxylate from the appropriate intermediates.

COMPOUND NAME	LCMS
Ethyl 4-(acetylamino)-2'--[(4-fluorophenyl)methyl] oxy}-5''-(trifluoromethyl)-1,1':2',1''-terphenyl-2-carboxylate	Rt=3.89, [MH <sup>-</sup> ] 550.1
Ethyl 4-(acetylamino)-2'--[(2,4-difluorophenyl)methyl] oxy}-5''-(trifluoromethyl)-1,1':2',1''-terphenyl-2-carboxylate	Rt=3.90, [MH <sup>-</sup> ] 568.1

Ethyl 2'-bromo-4-methyl-2-biphenylcarboxylate

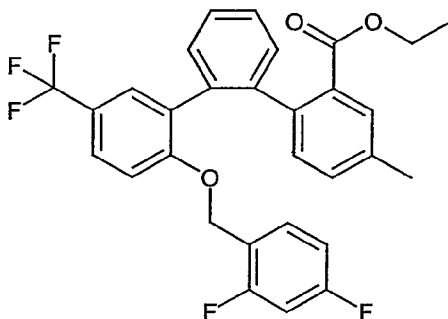
Prepared in a similar way to ethyl 4-(acetylamino)-2'-bromo-2-biphenylcarboxylate but using ethyl 2-bromo-5-methylbenzoate instead of ethyl 5-(acetylamino)-2-bromobenzoate. LC/MS  $t=3.77$ ,  $[MH^+]$  319.0

5 Ethyl 4-methyl-2'-[(phenylmethyl)oxy]-1,1':2,1''-terphenyl-2-carboxylate



10 Prepared in a similar way to ethyl 4-(acetylamino)-2'-[(phenylmethyl)oxy]-5''-(trifluoromethyl)-1,1':2,1''-terphenyl-2-carboxylate but using {2'-[(phenylmethyl)oxy]-2-biphenyl}boronic acid instead of [2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]boronic acid and ethyl 2'-bromo-4-methyl-2-biphenylcarboxylate instead of ethyl 4-(acetylamino)-2'-bromo-2-biphenylcarboxylate. LC/MS  $t=4.11$ ,  $[MH^+]$  423.1

15 ethyl 2'-{[(2,4-difluorophenyl)methyl]oxy}-4-methyl-5''-(trifluoromethyl)-1,1':2,1''-terphenyl-2-carboxylate



20 Prepared in a similar way to ethyl 4-(acetylamino)-2'-[(phenylmethyl)oxy]-5''-(trifluoromethyl)-1,1':2,1''-terphenyl-2-carboxylate but using [2'-{[(2,4-difluorophenyl)methyl]oxy}-5''-(trifluoromethyl)-2-biphenyl]boronic acid instead of [2-[(phenylmethyl)oxy]-5-(trifluoromethyl)phenyl]boronic acid and ethyl 2'-bromo-4-methyl-2-biphenylcarboxylate instead of ethyl 4-(acetylamino)-2'-bromo-2-biphenylcarboxylate.  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 0.89 (3H, t), 2.31 (3H, t), 3.95 (2H, q), 4.91 (2H, q), 6.77-7.55 (9H, m).

25 The following Examples 72-81 were prepared by the standard hydrolysis procedure (General Procedure D):

EXAMPLE	COMPOUND NAME	LC/MS	$^1H$ NMR
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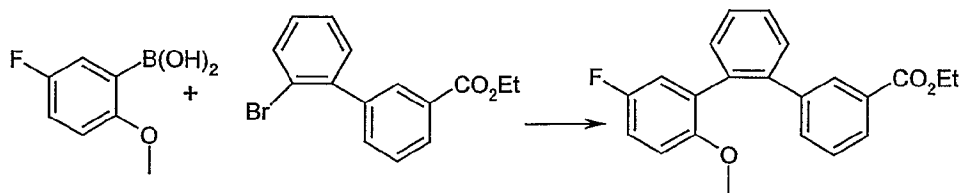


72	6-{5'-Chloro-2'-[(phenylmethyl)oxy]-2-biphenyl)-2-pyridinecarboxylic acid	Rt=3.61 [MH+] 416.3	(CDCl <sub>3</sub> ) 4.40-4.83 (2H, br d), 6.69 (1H, d, J=8Hz), 6.92-6.94 (2H, m), 7.20-7.29 (5H, m), 7.37-7.45 (2H, m), 7.51-7.56 (2H, m), 7.64-7.73 (2H, m), 7.99 (1H, d, J=8Hz)
73	6-(5'-Chloro-2'-{[(4-fluorophenyl)methyl]oxy}-2-biphenyl)-2-pyridinecarboxylic acid	Rt=3.62 [MH+] 434.3 436.3	(CDCl <sub>3</sub> ) 4.35-4.78 (2H, br d), 6.69 (1H, d, J=8Hz), 6.90-6.93 (4H, m), 7.21-7.28 (3H, m), 7.37-7.41 (2H, m), 7.53-7.56 (2H, m), 7.62-7.64 (1H, m), 7.72 (1H, t), 7.99 (1H, d, J=8Hz)
74	6-(5'-Chloro-2'-{[(2,4-difluorophenyl)methyl]oxy}-2-biphenyl)-2-pyridinecarboxylic acid	Rt=3.64 [MH+] 452.2 454.2	(CDCl <sub>3</sub> ) 4.43-4.78 (2H, br d), 6.67-6.76 (3H, m), 6.89 (1H, q), 7.23-7.28 (3H, m), 7.37-7.40 (2H, m), 7.53-7.55 (2H, m), 7.63-7.66 (1H, m), 7.74 (1H, t, J=8Hz), 8.00 (1H, d, J=8Hz)
75	2-[2'-{[(4-Fluorophenyl)methyl]oxy}-5'-(trifluoromethyl)-2-biphenyl]-4-pyridinecarboxylic acid	Rt=3.86 [MH+] 468.1	(DMSO-d <sub>6</sub> ) 4.65-5.10 (2H, br s), 7.09-7.11 (5H, m), 7.39-7.71 (8H, m), 8.61 (1H, d, J=5Hz), 13.4 (1H, br s)
76	3-Amino-6-[2'-{[(4-fluorophenyl)methyl]oxy}-5'-(trifluoromethyl)-2-biphenyl]-2-pyrazinecarboxylic acid	Rt=3.83 [MH+] 484.1	(DMSO-d <sub>6</sub> ) 4.65-5.10 (2H, br s), 7.05-7.15 (5H, m), 7.34-7.39 (3H, m), 7.46-7.54 (3H, m), 7.64 (1H, d, J=9Hz), 7.73 (1H, d, J=9Hz), 7.78 (1H, s), 12.8 (1H, br s)
77	4-(Acetylamino)-2'-[(phenylmethyl)oxy]-5'-(trifluoromethyl)-1,1':2',1''-terphenyl-2-carboxylic acid	Rt=3.56 [MH-] 504.0	(CDCl <sub>3</sub> ) 2.18 (3H, s), 4.78-4.95 (2H, m), 6.75 (1H, d, J=9Hz), 7.01-7.49 (14H, m), 7.80 (1H, dd, J=8Hz, 2Hz)

78	4-(Acetylamino)-2"-{[(4-fluorophenyl)methyl]oxy}-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-2-carboxylic acid	Rt=3.58 [MH-] 522.0	(CDCl <sub>3</sub> ) 2.18 (3H, s), 4.78-4.95 (2H, m), 6.74 (1H, d, J=9Hz), 6.90-7.09 (5H, m), 7.15 (1H, br s), 7.27- 7.50 (7H, m), 7.80 (1H, d, J=8Hz)
79	4-(Acetylamino)-2"-{[(2,4-difluorophenyl)methyl]oxy}-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-2-carboxylic acid	Rt=3.60 [MH-] 540.0	(DMSO-d <sub>6</sub> ) 2.02 (3H, s), 5.12 (2H, br d), 6.74 (1H, br d), 7.05-7.38 (9H, m), 7.50 (2H, dd), 7.89 (1H, d, J=2Hz), 10.0 (1H, s), 12.6 (1H, br s)
80	4-Methyl-2"-[(phenylmethyl)oxy]-1,1':2',1"-terphenyl-2-carboxylic acid	Rt=3.80 [MH-] 393.0	(DMSO-d <sub>6</sub> ) 2.26 (3H, s), 5.02 (2H, br s), 6.70 (1H, t), 6.79 (1H, d), 6.95-7.13 (5H, m), 7.25-7.34 (8H, m), 7.47 (1H, s), 12.5 (1H, br s)
81	2"-{[(2,4-Difluorophenyl)methyl]oxy}-4-methyl-5"-(trifluoromethyl)-1,1':2',1"-terphenyl-2-carboxylic acid	Rt=3.97 [MH-] 497.1	(DMSO-d <sub>6</sub> ) 2.26 (3H, s), 5.11 (2H, br q), 6.72 (1H, d), 6.79 (1H, d), 7.05-7.16 (3H, m), 7.23 (1H, d, J=9Hz), 7.26-7.44 (5H, m), 7.49-7.51 (2H, m), 12.6 (1H, br s)

### Preparation of Intermediates

#### 2-Methoxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid ethyl ester

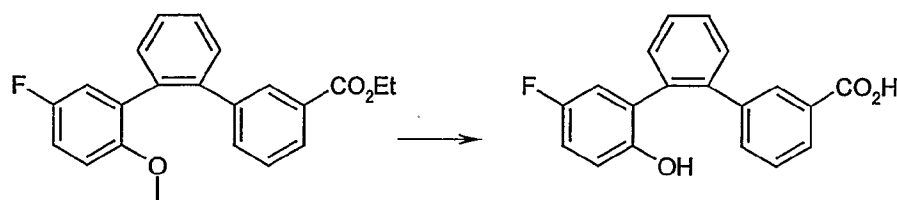


5

2'-Bromobiphenyl-3-carboxylic acid ethyl ester (1.53g, 5mmol), 2-methoxy-5-fluorophenylboronic acid (935mg, 5.5 mmol), tetrakis(triphenylphosphine) palladium(0) (580mg, 0.5mmol) and potassium carbonate (5.52g, 40mmol) were heated in toluene-ethanol(1:1, 50 ml) at 90°C for 3 hours. Upon cooling, the mixture was diluted with diethyl ether and water, the combined organic layers were dried(MgSO<sub>4</sub>), filtered and concentrated. The residue was purified by chromatography using Biotage® with 10% ethyl acetate in isohexane as eluent to yield the title compound (930mg).

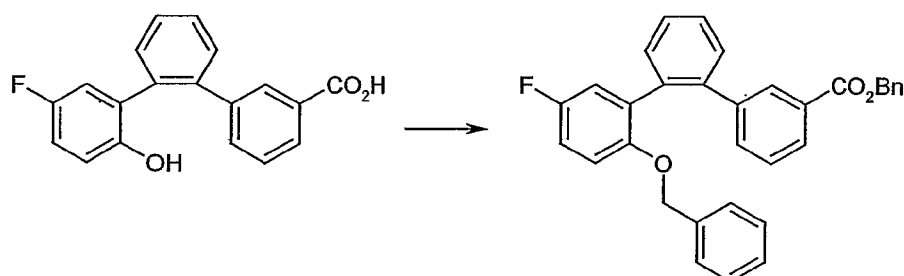
10

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.34(3H, t), 3.30(3H, s), 4.31(2H, q), 6.59(1H, dd), 6.89-6.92(2H, m), 7.23-7.27(2H, m), 7.37-7.45(4H, m), 7.87(1H, dd), 7.89(1H, s).

2-Hydroxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid

- 5 2-Methoxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid ethyl ester (930mg, 2.66mmol) was dissolved in dichloromethane (20ml), cooled to 0°C and 1M BBr<sub>3</sub> in dichloromethane (5.32ml, 5.32mmol) added dropwise at 0°C. The mixture was allowed to reach room temperature and stirred for 17 hours. The reaction was poured onto ice and extracted with diethyl ether which was washed with water, dried (MgSO<sub>4</sub>) and evaporated. The residue
- 10 was partitioned between isohexane and 2M sodium hydroxide solution and filtered. The aqueous layer was acidified with 2M hydrochloric acid solution and the product extracted into diethyl ether (x2), which was washed with water, dried (MgSO<sub>4</sub>) and evaporated to a cream foam (409mg)
- LC/MS Rt=3.40min [M-H]<sup>-</sup> 307

15

2-Benzyloxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid benzyl ester

- 20 2-Hydroxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid (136mg, 0.442mmol) was stirred in acetone (5ml) and potassium carbonate (183mg, 1.327mmol) added, followed by benzyl bromide (166mg, 116μl, 0.973mmol). The mixture was stirred at reflux for 16 hours. After cooling, diethyl ether and water were added and the organic phase washed with brine, dried (MgSO<sub>4</sub>) and evaporated to a clear oil (200mg).
- 25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.63(2H, br s), 5.27(2H, s), 6.61(1H, dd), 6.90-7.44(18H, m), 7.86(1H, s), 7.89(1H, dd).

30

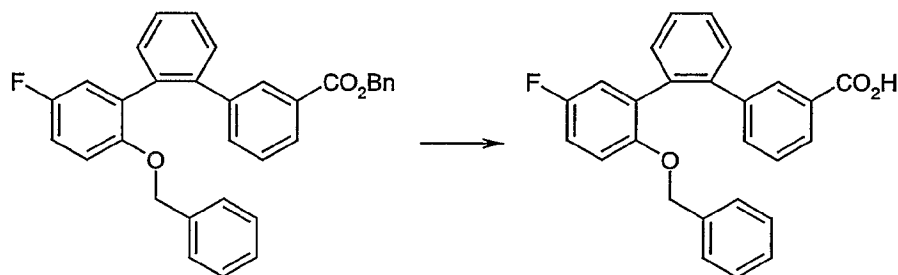
The following intermediates were prepared from the appropriate intermediates using a similar route to that used for the preparation of 2-Benzyloxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid benzyl ester

COMPOUND NAME

LCMS / <sup>1</sup>H NMR

2-(4-Fluorobenzyl)oxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid 4-fluorobenzyl ester	CDCl <sub>3</sub> δ: 4.66(2H, br s), 5.23(2H, s), 6.60(1H, dd), 6.90-7.44(16H, m), 7.81(1H, s), 7.87(1H, dd)
2-(2,4-Difluorobenzyl)oxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid 2,4-difluorobenzyl ester	CDCl <sub>3</sub> δ: 4.65(2H, br s), 5.29(2H, s), 6.69-7.44(15H, m), 7.80(1H, s), 7.87(1H, dd)

**Example 82 2-Benzyloxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid**



5

The compound was prepared by the standard hydrolysis procedure (General Procedure D). The residue was triturated with isohexane containing a trace of diethyl ether. The off-white solid was filtered and dried (87mg).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.71(2H, br s), 6.66(1H, dd), 6.82-6.92(2H, m), 7.01(2H, m), 7.22-7.46(9H, m), 7.91(2H, m), LC/MS Rt=3.87min [M-H] 433

10

The following Examples 83 and 84 were prepared from the appropriate ester by standard hydrolysis (General Procedure D).

EXAMPLE	COMPOUND NAME	LC/MS	<sup>1</sup> H NMR
83	2-(4-Fluorobenzyl)oxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid	Rt=3.89min [M-H] 415	CDCl <sub>3</sub> δ: 4.66(2H, br s), 6.66(1H, dd), 6.91-6.98 (6H, m), 7.22-7.26(2H, m), 7.39-7.47(4H, m), 7.90-7.93(2H, m)
84	2-(2,4-Difluorobenzyl)oxy-5-fluoro[1,1',2,2']terphenyl-3"-carboxylic acid	Rt=3.92min [M-H] 433	CDCl <sub>3</sub> δ: 4.65(2H, br s), 6.70-6.75(3H, m), 6.88-6.95(3H, m), 7.23-7.26(2H, m), 7.38-7.46(4H, m), 7.88-7.93(2H, m)

15

**Preparation of Intermediates**

3-Bromo-5-chloro-2-pyridinol

5-Chloro-2-pyridinol (5.18g, 40mmol) was dissolved in glacial acetic acid(50ml) and bromine (7.51g, 2.41ml, 47mmol) added. The mixture was stirred at room temperature for 48 hours. Ethyl acetate and water were added and the organic layer washed with water (x3), dried (MgSO<sub>4</sub>) and evaporated. The residue was triturated with diethyl ether and the buff solid filtered and dried (5.59g).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.52(1H, d J=3Hz), 7.87(1H, d J=3Hz).

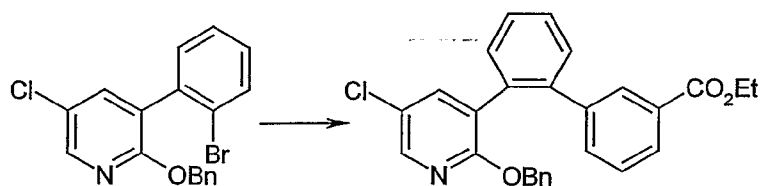
2-(Benzyloxy)-3-bromo-5-chloropyridine

3-Bromo-5-chloro-2-pyridinol (7.0g, 33.6mmol) was stirred in toluene (160ml) and silver carbonate (10.23g, 36.9mmol) added, followed by benzyl bromide (6.32g, 4.39ml, 36.9mmol). The mixture was heated to reflux for 1 hour. After cooling, the mixture was filtered, washed with water (x2), dried (MgSO<sub>4</sub>) and evaporated. The residue was triturated with isohexane and the pale yellow solid filtered and dried. (8.36g).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 5.43(2H, s), 7.32-7.48(5H, m), 7.82(1H, d J=2Hz), 8.04(1H, d J=2Hz).

3-(2-Bromophenyl)-5-chloro-2-(benzyloxy)pyridine

2-(Benzyloxy)-3-bromo-5-chloropyridine (150mg, 0.5mmol) and 2-bromophenylboronic acid (100mg, 0.5mmol) were dissolved in toluene/ethanol (1:1, 5ml) under nitrogen. Potassium carbonate (550mg, 4mmol) was added, followed by tetrakis(triphenylphosphine)palladium(0) (58mg, 0.05mmol). The resulting mixture was heated at 70°C in a Smithcreator® microwave for 10 minutes. After cooling, diethyl ether(10ml) and water (10ml) were added. The organic layer was washed with water, dried (MgSO<sub>4</sub>) and evaporated. The product was purified by flash chromatography (silica gel, 2% ethyl acetate: isohexane) to give the title compound as a clear oil (80mg).  
LC/MS Rt=4.14min [M+H]<sup>+</sup> 376

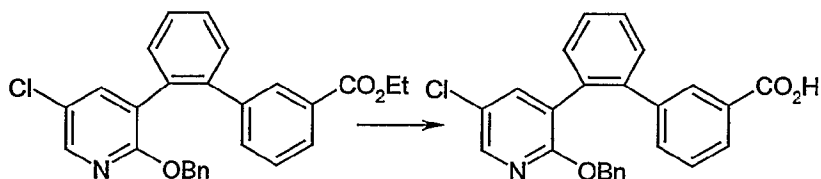
2'-{5-Chloro-2-(benzyloxy)-3-pyridinyl}-3-biphenylcarboxylic acid ethyl ester



3-(2-Bromophenyl)-5-chloro-2-(benzyloxy)pyridine (80mg, 0.214mmol) and 3-(carbethoxy)phenylboronic acid (42mg, 0.214mmol) were dissolved in toluene/ethanol (1:1 1ml) under nitrogen. Potassium carbonate (236mg, 1.71mmol) and tetrakis(triphenylphosphine)palladium(0) (25mg, 0.0214mmol) were added and the resulting mixture was heated at 70°C in a Smithcreator® microwave for 15 minutes. After cooling, diethyl ether (5ml) and water (5ml) were added. The organic layer was washed with water, dried (MgSO<sub>4</sub>) and evaporated. The product was purified by flash chromatography (silica gel, 2-3% ethyl acetate: isohexane) to give the title compound as a clear oil (31mg).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.34(3H, t  $J=4.5\text{Hz}$ ) 4.29 (2H, q  $J=4.5\text{Hz}$ ), 5.01(2H, br s), 7.09(2H, m), 7.18-7.26(5H, m), 7.37(1H, m), 7.42-7.46(4H, m), 7.81(1H, s), 7.87(1H, m), 8.00(1H, d  $J=2\text{Hz}$ ).

5 **Example 85: 2'-(5-Chloro-2-(benzyloxy)-3-pyridinyl)-3-biphenylcarboxylic acid**



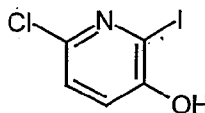
The compound was prepared by the standard hydrolysis procedure. The residue was triturated with isohexane. The off-white solid was filtered and dried (8.4mg).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.03(2H, br s), 7.11(2H, m), 7.21-7.26(5H, m), 7.37(1H, m), 7.44-7.47(4H, m), 7.89(1H, s), 7.91(1H, m), 8.01(1H, d  $J=2\text{Hz}$ ).

LC/MS  $R_t=4.00\text{min}$   $[M+H]^+$  416.

15 **Preparation of Intermediates**

**6-Chloro-2-iodo-3-pyridinol**

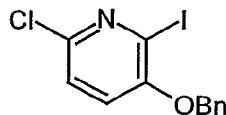


20 6-Chloro-3-pyridinol (2.0g, 15.44mmol) was stirred in water (40ml) containing sodium carbonate (3.43g, 32.36mmol) and iodine (3.92g, 15.44mmol) was added. The mixture was stirred at room temperature for 72 hours. The pH was adjusted to pH8 with 1M hydrochloric acid solution and the mixture extracted with ethyl acetate (x2). The combined organic extracts were washed with brine and dried ( $\text{MgSO}_4$ ). The aqueous layer was

25 acidified to pH5 with 1M hydrochloric acid solution and extracted with ethyl acetate, which was washed with brine, dried ( $\text{MgSO}_4$ ) and the combined solutions evaporated to leave the title compound as a buff solid (3.70g).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.18 (1H, d,  $J=2.5\text{Hz}$ ), 7.31 (1H, d,  $J=2.5\text{Hz}$ ), 9.53 (1H, br s).

30 **6-Chloro-2-iodo-3-[(phenylmethyl)oxy]pyridine**

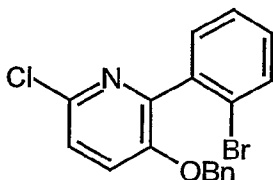


6-Chloro-2-iodo-3-pyridinol (1.28g, 5mmol) and silver carbonate (1.52g, 5.5mmol) were dissolved in toluene (25ml) and benzyl bromide (654 $\mu\text{l}$ , 5.5mmol) added. The mixture was

35 heated to reflux under nitrogen for 1 hour. After cooling, the mixture was filtered, washed

with water (x2), dried ( $\text{MgSO}_4$ ) and evaporated to an orange oil which was flash chromatographed eluting with 5% ethyl acetate in isohexane to give the title compound as an oil which crystallised on standing. LC/MS  $t = 3.70$ ,  $[\text{MH}^+]$  346, 348.

5 2-(2-Bromophenyl)-6-chloro-3-[(phenylmethyl)oxy]pyridine



10 6-Chloro-2-iodo-3-[(phenylmethyl)oxy]pyridine (346mg, 1mmol) and 2-bromophenylboronic acid (201mg, 1mmol) were dissolved in 1:1 toluene/ethanol (10ml) and potassium carbonate (1.1g, 8mmol) and tetrakis(triphenylphosphine) palladium(0) (116mg, 0.1mmol) added. The mixture was stirred under nitrogen and heated at  $90^\circ\text{C}$  for 2 hours. After cooling, diethyl ether and water were added and the organic layer washed with water,  
 15 10% ethyl acetate/isohexane to give the title compound as a clear oil (308mg)  
 LC/MS  $t = 3.77$ ,  $[\text{MH}^+]$  376, 378.

The following intermediates were prepared from the appropriate precursors using a similar route to that used for the preparation of 2'-[5-Chloro-2-(benzyloxy)-3-pyridinyl]-3-biphenylcarboxylic acid ethyl ester  
 20

COMPOUND NAME	LCMS
Ethyl 2'-[6-chloro-3-[(phenylmethyl)oxy]-2-pyridinyl]-3-biphenylcarboxylate	Rt=3.97 $[\text{MH}^+]$ 444,446
Methyl 5-amino-2'-[6-chloro-3-[(phenylmethyl)oxy]-2-pyridinyl]-3-biphenylcarboxylate	Rt=3.61 $[\text{MH}^+]$ 445,447

The following Examples 86 and 87 were prepared from the appropriate ester by standard hydrolysis (General Procedure D).

25

EXAMPLE	COMPOUND NAME	LC/MS	$^1\text{H}$ NMR
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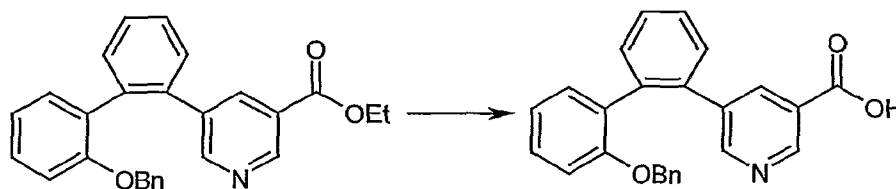
86	2'-{6-Chloro-3-[(phenylmethyl)oxy]-2-pyridinyl}-3-biphenylcarboxylic acid	Rt=3.68 [MH <sup>+</sup> ] 416, 418	CDCl <sub>3</sub> : 4.61(2H, s), 6.91-6.93 (3H, m), 7.12(1H, d, J=3Hz), 7.23-7.26(5H, m), 7.43-7.57(4H, m), 7.93-7.94(2H, m)
87	5-Amino-2'-{6-chloro-3-[(phenylmethyl)oxy]-2-pyridinyl}-3-biphenylcarboxylic acid	Rt=3.38 [MH <sup>+</sup> ]431, 433	CDCl <sub>3</sub> : 4.67(2H, s), 6.59(1H, s), 6.95-6.97(3H, m), 7.11-7.12(1H, d, J=3Hz), 7.24-7.30(5H, m), 7.40-7.53(4H, m)

**Example 88 5-{2'-[(Phenylmethyl)oxy]-2-biphenyl}-3-pyridinecarboxylic acid**

**a) Ethyl 5-{2'-[(phenylmethyl)oxy]-2-biphenyl}-3-pyridinecarboxylate**

- 5 A mixture of ethyl 5-bromonicotinate (46mg, 0.2mmol), {2'-[(phenylmethyl)oxy]-2-biphenyl}boronic acid (61mg, 0.2mmol), potassium carbonate (221mg, 1.6mmol) and tetrakis(triphenylphosphine)palladium(0) (23mg, 0.02mmol) was stirred and heated at 90°C under nitrogen for 2 hours. After cooling the mixture was diluted with ether/water and the organic phase dried (magnesium sulphate), evaporated and chromatographed on silica eluting with ethyl acetate/iso-hexane (1:5) to give 66mg of colourless gum.
- 10 LC/MS t=3.84, [MH<sup>+</sup>] 410.2.

**b) 5-{2'-[(Phenylmethyl)oxy]-2-biphenyl}-3-pyridinecarboxylic acid**



- 15 Prepared from ethyl 5-{2'-[(phenylmethyl)oxy]-2-biphenyl}-3-pyridinecarboxylate using the standard hydrolysis procedure.
- LC/MS t=3.60, [MH<sup>+</sup>] 382.2.

**Example 89 4''-Chloro-2''-[(phenylmethyl)oxy]-1,1':2',1''-terphenyl-2-carboxylic acid**

20

**a) 1-Bromo-4-chloro-2-[(phenylmethyl)oxy]benzene**

- A mixture of 2-bromo-5-chlorophenol (3.93g, 18.94mmol), benzyl bromide (3.42g, 20mmol) and potassium carbonate (10g, 72.46mmol) in acetone (80ml) was stirred and refluxed for 3 hours then cooled, evaporated and dissolved in ether/water. The organic phase was dried (magnesium sulphate) evaporated and purified by chromatography on silica eluting with ethyl acetate/iso-hexane (1:99) to give 5.51g of white solid.
- 25



$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 5.13 (2H, s), 6.84 (1H, dd,  $J=8\text{Hz}$ ,  $2\text{Hz}$ ), 6.93 (1H, d,  $J=2\text{Hz}$ ), 7.34-7.48 (6H, m).

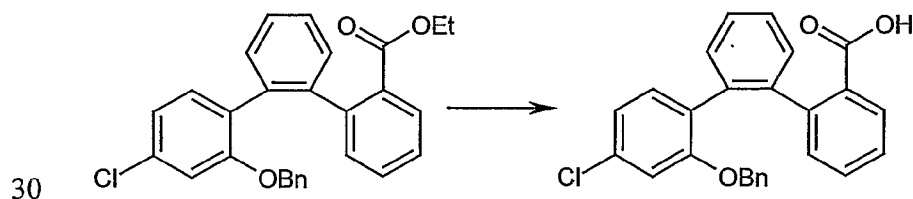
**b) {4-Chloro-2-[(phenylmethyl)oxy]phenyl}boronic acid**

- 5 1-bromo-4-chloro-2-[(phenylmethyl)oxy]benzene (2.976g, 10mmol) in dry tetrahydrofuran (40ml) was cooled to  $-100^\circ\text{C}$ . n-Butyl lithium, 1.6M solution in hexanes (6.9ml, 11mmol) was added dropwise over 10min under nitrogen. The reaction mixture was then allowed to warm to  $-70^\circ\text{C}$  for 1h. Triisopropylborate (5.514, 30mmol) was added dropwise under nitrogen. The cooling bath was then removed and the reaction mixture was allowed to
- 10 warm to room temperature before being quenched with 2N hydrochloric acid (30mL) and stirred vigorously at room temperature for 1h. The product was then extracted with ether, dried over magnesium sulphate and evaporated down to an oil which was dissolved in iso-hexane and the solid which separated out was filtered off and dried. Yield 1.89g.
- $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 5.11 (2H, s), 5.79 (2H, s), 6.99 (1H, d,  $J=2\text{Hz}$ ), 7.04 (1H, dd,  $J=8\text{Hz}$ ,  $2\text{Hz}$ ), 7.37-7.43 (5H, m), 7.79 (1H, d,  $J=8\text{Hz}$ ).
- 15

**c) Ethyl 4"-chloro-2"-[(phenylmethyl)oxy]-1,1':2,1"-terphenyl-2-carboxylate**

- A mixture of ethyl 2'-bromo-2-biphenylcarboxylate (153mg, 0.5mmol), {4-chloro-2-[(phenylmethyl)oxy]phenyl}boronic acid (144mg, 0.55mmol), potassium carbonate (552mg, 4mmol) and tetrakis(triphenylphosphine)palladium(0) (58mg, 0.05mmol) was stirred and
- 20 heated at  $90^\circ\text{C}$  under nitrogen for 18 hours. After cooling the mixture was diluted with ether/water and the organic phase dried (magnesium sulphate), evaporated and chromatographed on silica eluting with ethyl acetate/iso-hexane (1:19) to give 104mg of colourless gum.
- $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.95 (3H, br s), 3.98 (2H, br s), 4.87 (2H, q), 6.74 (1H, dd,  $J=8\text{Hz}$ ,  $2\text{Hz}$ ), 6.77 (1H, d,  $J=2\text{Hz}$ ), 6.89-7.05 (2H, m), 7.18-7.39 (11H, m), 7.71 (1H, m).
- 25

**d) 4"-Chloro-2"-[(phenylmethyl)oxy]-1,1':2,1"-terphenyl-2-carboxylic acid**

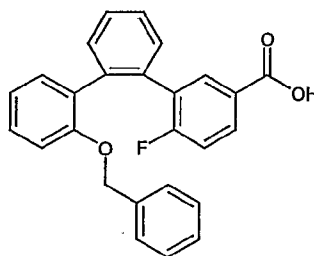


The title compound was prepared from ethyl 4"-chloro-2"-[(phenylmethyl)oxy]-1,1':2,1"-terphenyl-2-carboxylate using the standard hydrolysis procedure.

LC/MS  $t=3.60$ ,  $[\text{MH}]^-$  413.1, 415.1

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**Example 90 6"-Fluoro-2-benzyloxy- [1,1';2,1'']terphenyl-3"-carboxylic acid**



- {2'-[(phenylmethyl)oxy]-2-biphenyl}boronic acid (60mg, 0.19 mmol) and 3-bromo-4-fluorobenzoic acid (69mg, 0.31 mmol) were dissolved in 1:1 toluene:ethanol (6ml) under nitrogen. Potassium carbonate (290mg, 2.1mmol) and
- 5 tetrakis(triphenylphosphine)palladium(0) (23mg, 0.019mmol) were added and the mixture heated at 90°C for 1h. After cooling, the reaction mixture was poured into water, acidified with 1M HCl solution and extracted with ethyl acetate (15 x 2ml), the combined organic layer were dried and evaporated. The residue was then purified on an SPE column using 40% of ethyl acetate in iso-hexane to give the title compound as white solid.
- 10 LC/MS t=3.84, [MH-] 397,398

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

#### 15 ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compounds of formula (I) can be tested using the following assays to demonstrate their prostanoid antagonist or agonist activity in vitro and in vivo and their selectivity. The prostaglandin receptors investigated are DP, EP<sub>1</sub>, EP<sub>2</sub>, EP<sub>3</sub>, EP<sub>4</sub>, FP, IP and TP.

- 20 The ability of compounds to antagonise EP<sub>1</sub> & EP<sub>3</sub> receptors may be demonstrated using a functional calcium mobilisation assay. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ([Ca<sup>2+</sup>]<sub>i</sub>) in response to activation of EP<sub>1</sub> or EP<sub>3</sub> receptors by the natural agonist hormone
- 25 prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of PGE<sub>2</sub> can mobilise. The net effect is to displace the PGE<sub>2</sub> concentration-effect curve to higher concentrations of PGE<sub>2</sub>. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing
- 30 amounts of [Ca<sup>2+</sup>]<sub>i</sub> produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software.

- 35 The human EP<sub>1</sub> or EP<sub>3</sub> calcium mobilisation assay (hereafter referred to as 'the calcium assay') utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing either EP<sub>1</sub> or EP<sub>3</sub> cDNA has previously been transfected. Cells are cultured in

suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin and 10µg/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 384-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing fluo-3 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of PGE<sub>2</sub> are then added to the plate in order to assess the antagonist properties of the compounds.

The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by PGE<sub>2</sub> (pIC<sub>50</sub>) may then be estimated.

#### Binding Assay for the Human Prostanoid EP<sub>1</sub> Receptor

Competition assay using [<sup>3</sup>H]-PGE<sub>2</sub>.

Compound potencies are determined using a radioligand binding assay. In this assay compound potencies are determined from their ability to compete with tritiated prostaglandin E<sub>2</sub> ([<sup>3</sup>H]-PGE<sub>2</sub>) for binding to the human EP<sub>1</sub> receptor.

This assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing the EP<sub>1</sub> cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin, 10µg/ml puromycin and 10µM indomethacin.

Cells are detached from the culture flasks by incubation in calcium and magnesium free phosphate buffered saline containing 1 mM disodium ethylenediaminetetraacetic acid (Na<sub>2</sub>EDTA) and 10µM indomethacin for 5 min. The cells are isolated by centrifugation at 250xg for 5mins and suspended in an ice cold buffer such as 50 mM Tris, 1mM Na<sub>2</sub>EDTA, 140mM NaCl, 10µM indomethacin (pH 7.4). The cells are homogenised using a Polytron tissue disrupter (2x10s burst at full setting), centrifuged at 48,000xg for 20mins and the pellet containing the membrane fraction is washed three times by suspension and centrifugation at 48,000xg for 20mins. The final membrane pellet is suspended in an assay buffer such as 10mM 2-[N-morpholino]ethanesulphonic acid, 1mM Na<sub>2</sub>EDTA, 10mM MgCl<sub>2</sub> (pH 6). Aliquots are frozen at -80°C until required.

For the binding assay the cell membranes, competing compounds and [<sup>3</sup>H]-PGE<sub>2</sub> (3nM final assay concentration) are incubated in a final volume of 100µl for 30 min at 30°C. All

reagents are prepared in assay buffer. Reactions are terminated by rapid vacuum filtration over GF/B filters using a Brandell cell harvester. The filters are washed with ice cold assay buffer, dried and the radioactivity retained on the filters is measured by liquid scintillation counting in Packard TopCount scintillation counter.

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The data are analysed using non linear curve fitting techniques (GraphPad Prism 3) to determine the concentration of compound producing 50% inhibition of specific binding ( $IC_{50}$ ).

- 10 By application of these techniques, compounds of the Examples had an antagonist  $pIC_{50}$  value of 6.0 to 9.0 at  $EP_1$  receptors and  $pIC_{50}$  value of  $< 6.0$  at  $EP_3$  receptors.

No toxicological effects are indicated/expected when a compound (of the invention) is administered in the above mentioned dosage range.

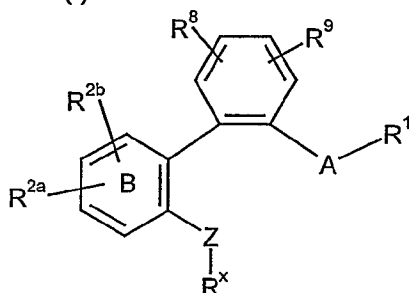
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The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein.

- 20 They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

## CLAIMS

1. A compound of formula (I):



(I)

5 wherein:

A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

B represents a phenyl or pyridyl ring;

Z represents O, S, SO, or SO<sub>2</sub>;

10 R<sup>1</sup> represents CO<sub>2</sub>R<sup>4</sup>, CN, CONR<sup>5</sup>R<sup>6</sup>, CH<sub>2</sub>CO<sub>2</sub>R<sup>4</sup>, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO<sub>2</sub>alkyl, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>CONR<sup>5</sup>R<sup>6</sup>, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

R<sup>2a</sup> and R<sup>2b</sup> independently represents hydrogen, halogen, optionally substituted alkyl,

15 optionally substituted alkoxy, CN, SO<sub>2</sub>alkyl, SR<sup>5</sup>, NO<sub>2</sub>, optionally substituted aryl, CONR<sup>5</sup>R<sup>6</sup> or optionally substituted heteroaryl;

R<sup>x</sup> represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR<sup>4</sup>, O and SO<sub>n</sub>, wherein n is 0, 1 or 2; or R<sup>x</sup> represents optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocyclyl, optionally

20 substituted CQ<sup>a</sup>Q<sup>b</sup>-bicyclic heterocyclyl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-aryl;

R<sup>4</sup> represents hydrogen or an optionally substituted alkyl;

R<sup>5</sup> represents hydrogen or an optionally substituted alkyl;

R<sup>6</sup> represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO<sub>2</sub>aryl, optionally substituted SO<sub>2</sub>alkyl, optionally substituted

25 SO<sub>2</sub>heteroaryl, CN, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>aryl, optionally substituted CQ<sup>a</sup>Q<sup>b</sup>heteroaryl or COR<sup>7</sup>;

R<sup>7</sup> represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

R<sup>8</sup> and R<sup>9</sup> independently represent hydrogen, chloro, fluoro, CF<sub>3</sub>, C<sub>1-3</sub>alkoxy or C<sub>1-3</sub>alkyl;

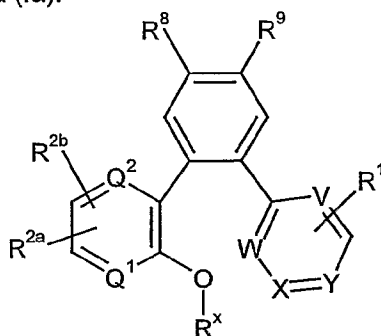
30 Q<sup>a</sup> and Q<sup>b</sup> are independently selected from hydrogen and CH<sub>3</sub>;

wherein when A is a 6-membered ring the R<sup>1</sup> substituent and phenyl ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R<sup>1</sup> substituent and phenyl ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;

and derivatives thereof;

provided that the compound is not 2-benzyloxy[1,1';2',1'']terphenyl-4''-carboxylic acid.

2. A compound according to claim 1 wherein when A is a 6-membered ring, the R<sup>1</sup> substituent and phenyl ring are attached to carbon atoms 1,2-, or 1,3- relative to each other.
3. A compound according to claim 1 or claim 2 wherein A is phenyl, pyridyl, or pyrazinyl.
4. A compound of formula (Ia):



(Ia)

wherein:

- W, X, and Y each represents CR<sup>12</sup> or N;
- V represents CR<sup>1</sup>, CR<sup>12</sup> or N;
- wherein at least two of W, X, Y or V is CR<sup>12</sup>; and R<sup>12</sup> is independently selected from hydrogen, halogen, CN, optionally substituted CO<sub>2</sub>C<sub>1-6</sub>alkyl, CONR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>R<sup>6</sup>, optionally substituted NR<sup>5</sup>COC<sub>1-6</sub>alkyl, optionally substituted NR<sup>5</sup>Cophenyl, optionally substituted NR<sup>5</sup>COpiperidiny, optionally substituted NR<sup>5</sup>COheterocycl, optionally substituted NR<sup>5</sup>SO<sub>2</sub>C<sub>1-6</sub>alkyl, OH, optionally substituted OC<sub>1-6</sub>alkyl, optionally substituted C<sub>1-6</sub>alkyl and NR<sup>10</sup>R<sup>11</sup>;
- Q<sup>1</sup> and Q<sup>2</sup> each represents CH, or one of Q<sup>1</sup> and Q<sup>2</sup> is N and the other is CH;
- R<sup>1</sup> is CO<sub>2</sub>H, optionally substituted CONHSO<sub>2</sub>aryl, CH<sub>2</sub>CO<sub>2</sub>H, SO<sub>2</sub>NHCOR<sup>7</sup>, SO<sub>2</sub>NHCOC<sub>1-6</sub>alkyl or tetrazolyl and is positioned 1,2-, or 1,3- relative to the phenyl ring;
- R<sup>2a</sup> and R<sup>2b</sup> are independently selected from hydrogen, halo, or CF<sub>3</sub>;
- R<sup>x</sup> represents optionally substituted C<sub>1-6</sub>alkyl, or R<sup>x</sup> represents optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-heterocycl or optionally substituted CQ<sup>a</sup>Q<sup>b</sup>-phenyl wherein Q<sup>a</sup> and Q<sup>b</sup> are independently selected from hydrogen and CH<sub>3</sub>;
- R<sup>4</sup> represents hydrogen or an optionally substituted C<sub>1-6</sub>alkyl;
- R<sup>5</sup> represents hydrogen or an optionally substituted C<sub>1-6</sub>alkyl;
- R<sup>6</sup> represents hydrogen or an optionally substituted C<sub>1-6</sub>alkyl, optionally substituted SO<sub>2</sub>phenyl, optionally substituted SO<sub>2</sub>heterocycl group, CN, optionally substituted CH<sub>2</sub>phenyl or COR<sup>7</sup>;
- R<sup>7</sup> represents hydrogen, optionally substituted heteroaryl or optionally substituted phenyl;
- R<sup>8</sup> and R<sup>9</sup> independently represent hydrogen, chloro, fluoro, CF<sub>3</sub>, C<sub>1-3</sub>alkoxy or C<sub>1-3</sub>alkyl;
- and

R<sup>10</sup> and R<sup>11</sup> together with the nitrogen atom to which they are attached form a morpholine ring, a 5- or 6-membered lactam ring or a 5- or 6-membered cyclic sulphonamide, and derivatives thereof.

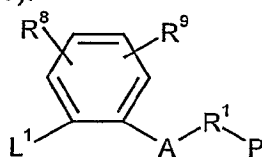
- 5     5.     A compound according to any one of claims 1 to 4 wherein R<sup>x</sup> is optionally substituted C<sub>1-8</sub>alkyl, optionally substituted CH<sub>2</sub>phenyl, CH<sub>2</sub>pyridyl, or CH<sub>2</sub>thienyl.
6.     A compound according to any one of claims 1 to 5 wherein R<sup>2b</sup> is positioned 1,4- relative to the Z substituent and 1,3- relative to the phenyl ring.
- 10     7.     A compound selected from the compounds of Examples 1-90 or a derivative thereof.
8.     A pharmaceutical composition comprising a compound according to any one of
- 15     claims 1 to 7 or a pharmaceutically acceptable derivative thereof together with a pharmaceutical carrier and/or excipient.
9.     A compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof for use as an active therapeutic substance.
- 20     10.     A compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors.
- 25     11.     A method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors which comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof.
- 30     12.     A method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof.
- 35     13.     A method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof.
- 40     14.     Use of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE<sub>2</sub> at EP<sub>1</sub> receptors.

15. Use of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder.

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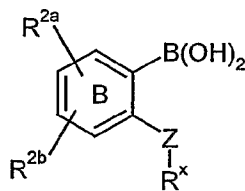
16. Use of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

- 10 17. A process for the preparation of a compound of formula (I) as defined in claim 1 or a derivative thereof comprising:  
reacting a compound of formula (IV):



(IV)

- 15 wherein  $R^8$ ,  $R^9$ , A, and  $R^1$  are as hereinbefore defined above for a compound of formula (I),  $L^1$  is a leaving group and P is an optional protecting group;  
with a compound of formula (III):



(III)

- 20 wherein  $R^{2a}$ ,  $R^{2b}$ , B, Z, and  $R^x$  are as hereinbefore defined above for a compound of formula (I);  
and where required converting:  
one group A to another group A, and/or  
one group  $R^x$  to another group  $R^x$ ;  
25 and where required carrying out the following optional steps in any order:  
effecting deprotection; and/or  
converting one group  $R^1$  to another group  $R^1$ ; and/or  
forming a derivative of the compound of formula (I) so formed.
- 30 18. A compound of formula (I) or a derivative thereof, according to claim 1, substantially as hereinbefore described with reference to any one of the Examples.